

SPECIALTIES IN SCIENCE: A SOCIOLOGICAL STUDY OF X-RAY CRYSTALLOGRAPHY

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NOTE ON REFERENCES

References in the text are normally of the form (Ewald :1962a: 25). The full title of the reference is given in the "Work Cited", where the arrangement is in alphabetical order. In the above example, Ewald refers to the author's name, 1962a refers to the date of publication of the work in question (a, b, etc. being employed when more than one paper was published by the author in a single year), and 25 refers to the page number. In some places the name of the author appears in the text, and only the date and page number are given in brackets after the author's name.

DECLARATION

I have composed this thesis myself, and the work in it is my own.



SUMMARY

Data concerning the development of ideas in the scientific specialty of X-ray crystallography (and protein X-ray crystallography in particular) is presented. Certain literature in the sociology of science is reviewed, and the work of Kuhn and some of his sociological interpreters is discussed in detail.

From this background, an attempt is made to understand some aspects of the development of ideas in parts of X-ray crystallography. The notion of "specialty" is defined, and it is suggested, after Kuhn, that scientific knowledge in the specialty may be seen as normative. However, certain distinctions between some sociological usages of the term "norm", and Kuhn's use of the terms "paradigm", "exemplar" and "disciplinary matrix" are outlined, and the latter terms are found to be more useful in understanding scientific innovation.

The question is then asked: how are the areas of scientific activity chosen by the actors in a given specialty? Why do they work in these areas, and not in others? No final answer is offered, but certain categories and relationships between those categories are distinguished. Thus, technique, theory, and problem based specialties are defined. Technique based specialties are seen as groups of actors who have internalised and used sets of exemplars that primarily concern methods -- in this type of specialty actors work first and foremost on the development of methods. In theory based specialties, theoretical development and innovation are the first concern. Problem based specialties are defined as constituting communicating groups of scientists who are concerned with the same or similar problems, who yet share only poorly specified exemplary guides to²¹

scientific action.

Finally, it is suggested that in a technique based specialty, standards of acceptable scientific action are most clearly specified in relation to methods, and that a less well defined set of attitudes concern the subject matters of work chosen. It is further argued that X-ray crystallography may be seen as an example of a technique based specialty.

1 INTRODUCTION

This thesis does two major things. Firstly it offers some detailed data on the development of a particular aspect of X-ray crystallography -- that of British protein crystallography. Secondly it attempts a description of some of the salient features of protein crystallography by developing a theoretically oriented scheme. The theoretical scheme involves the use of a certain number of new terms, and these are defined. Having defined these terms, the scheme then addresses itself primarily to the question -- what constitutes an explanation for the direction of scientific growth?

Perhaps this question needs a little justification. At first sight the direction of scientific growth may seem to be unproblematical -- the development of science attracts, after the event, an aura of inevitability that I believe to be quite false. It becomes clear that it is false whenever the observer steps outside a positivist world view. For the positivist might argue (crudely) that the history of science represents the development of correct theories and observations, and the sweeping away of various kinds of error. In this view science has now achieved, in all probability, a state where most of the errors have now been removed, and theories are being developed based on correct observations. If one happens to believe, with the positivists, that there is one correct way of understanding the world, then the problem of the nature of scientific growth is perhaps less problematical.

If, on the other hand, one takes the view that theory building is an active process, involving the placing of constructs on selected data, then the question immediately arises in full force -- why do we have these constructs and not others? Why, in other words, has science grown in the direction that it has actually taken?

The scheme that is developed at the end of this thesis is by no means a final answer to these questions. It hardly considers "externalist" factors in the history of science, for example, and it represents only a small development of an internalist viewpoint. It indicates where we must look for explanations, rather than by itself explaining the direction of scientific growth. It demands data of certain sorts that have still to be collected. On the other hand it is, in the last analysis, a sociological explanation. It is one of the fundamental assumptions that science, as an activity, is amenable to sociological explanation, in just the same way as any other aspect of human activity. The scheme seeks to examine the knowledge of science as normative, and its change as amenable to group pressures and beliefs.

This work grows, very obviously, from the work of T.S. Kuhn. Kuhn, although not himself a sociologist, offers an explanation of scientific change and growth that is in the first instance sociological. Science is not a system of abstract ideas whose operations can only be understood by philosophers. It is, in his view, a group activity, which involves consensus, disensus, and periodic upheavals. In this thesis the major part of Kuhn's work has not been discussed. The author does not wish, at the moment or in the foreseeable future, to commit himself to general theories about scientific change. He wishes, rather, to carry out detailed empirical studies in a number of different areas of science in order to develop a number of different case studies. This work, on protein crystallography can be seen as a first study -- all be it a pilot study.

A word on the origins of this work is in order. Four years ago the author was accepted into the Science Studies Unit to carry out a

study of disciplinary differentiation. Casting around rather at random, it was decided that molecular biology constituted a suitable area of study. When the author came to look at molecular biology, it became clear that it was in fact an unsatisfactory area for a number of reasons. The most important of these was quite simply, its size. A detailed study of the type required was quite beyond the range of possibility given the time and manpower available. A further difficulty involved the definition of molecular biology. Not only was it not easy to define where molecular biology ended and neighbouring disciplines started, but furthermore it was not even immediately clear how one should ask this question about disciplinary boundaries so that it made sense and was answerable.

As a result of these factors, the author concentrated on one relatively easily identified strand of modern molecular biology -- that of British X-ray diffraction work on proteins. The work of the last three years is in part reported in what follows. Much work was carried out, however, which does not appear in these pages. The waste of effort was perhaps, inevitable, in an area where the guidelines were so few and far between. There were no paradigmatic studies of the growth of specialties in the literature, and this resulted in confusion on at least two major scores. Firstly, it was not clear how much detail, and how wide ranging the study should be. The result is that the author has detailed data of many aspects of the history of X-ray crystallography, which although written up into thesis form, have been excluded on grounds of both relevance and length. Secondly, it was not clear what kinds of data would be relevant in the last analysis. It seemed obvious that a detailed knowledge of the development of ideas would be important, and so it has turned out to be. But it was not so clear, at least at the time, to what extent, and in what way,

data about the social structure and interaction patterns should be collected. The result is that in the final writing up, the network data have not been sufficient to allow a full illustration of the scheme developed at the end of the thesis, and this will have to wait for further work. However, the relevance of the theoretical scheme to a description of X-ray crystallography has, I believe, been demonstrated in large part.

I owe an immense debt, if not to Thomas Kuhn in person, then to his writings. I view this work as an "articulation" of a small part of his general world view. There is also much in this thesis that rests on the work of Warren Hagstrom, whose book The Scientific Community has by turns delighted and infuriated me during the last four years. The debt I owe to my colleagues is different, but just as great. In particular I would like to mention Barry Barnes and David Bloor who have contributed greatly to my outlook. I have also, during the course of this work, had long conversations with Tom Elsdale, David French, Mike Mulkay, and Nick Mullins, who have contributed greatly to my understanding of the area. My supervisors, David Edge and Tony Coxon have had to bear the brunt of the ongoing research process and I am deeply grateful to them.

My last acknowledgement must be reserved for the X-ray crystallographers, molecular biologists, biochemists and others who agreed to be interviewed during the course of this research. It would be invidious to pick out just a few, for they range from young and unknown, to the eminent. Some have been quoted in the text, but most have not. They have shared one thing in common -- a high commitment to the pursuit of truth, even to the extent of helping an investigator such as myself by talking, on many occasions for several hours, about their work, and their attitudes to science. I thank them.

Unfortunately, none of the above can be described as being in any way responsible for the work as it has been carried out, although it has been improved immeasurable through their many suggestions. Therefore, I must take full responsibility for what follows.

2 EARLY HISTORY OF X-RAY CRYSTALLOGRAPHY

The aim of this chapter is to summarise the social and academic achievements of British X-ray crystallography up until 1939. This will be done in order to provide an intellectual and social context in which the more detailed history of protein X-ray crystallography may be viewed.

2.1 Intellectual Origins

Röntgen discovered X-rays in 1895, accidentally, while carrying out experiments on cathode rays. He studied the phenomenon, and discovered a number of characteristic properties: that they travelled in straight lines; that they were absorbed by matter; that they ionized air; that certain targets were more effective producers of X-rays than others. Although the medical implications of X-rays were widely exploited scientific understanding was slow to grow. Ewald (:1962:11) notes that the following discoveries were made between 1895 and 1912

- (1) The polarisation of X-rays (Barkla, 1905).
- (2) The discovery of the "characteristic" X-rays (Barkla).
- (3) The discovery of the photoelectric effect, and an estimate of the wavelength of X-rays (Wein, 1907).
- (4) The discovery of the diffraction of X-rays by a slit (Walter & Pohl, 1908-09).

Much of the debate about X-rays concerned their nature -- were they a wave phenomenon, or were they corpuscular? Barkla was a strong proponent of the wave theory, and W.L. Bragg of the corpuscular theory.

Although the intellectual origins of X-ray crystallography lie partly in this tradition, they also come, in part, from crystallography. Classical crystallography has a long history (see Burke: 1966), partly concerned with the description and measurement of crystals, and partly

with the development of the laws of symmetry. Final development of the latter was achieved by Schoenflies, in 1891, who described the 230 possible space groups that became the basis for modern crystallography, both X-ray and morphological. The fact that all possible types of symmetry that could be constructed by fitting together equal particles had been described did not mean that crystallographers had any developed theories about the nature of the equal particles. The best developed theory in 1912, although it was speculative only, was that developed by Taumann (Göttingen), and Barlow and Pope (Cambridge), who visualised atoms of characteristic diameters packed together so as to touch one another.

2.2 The Discovery of X-ray Diffraction

The original idea that X-rays might be diffracted by crystal structures in an interpretable way grew out of a discussion between Ewald, a Ph.D. student at Munich, and Laue, a professor. Ewald raised a problem with Laue in connection with his thesis, and in so doing introduced Laue to the work of the classical crystallographers -- notably Groth. Laue became aware of the possibility of X-ray diffraction in crystals, and after some discussion with other workers, many of whom were quite skeptical about its possibility, two young assistants, Friedrich and Knipping, undertook an experiment to see if it could be detected. On the second attempt the first X-ray diffraction effect was recorded, and Laue realised that a rough explanation of the shape of the diffraction effect could be given if the theory of diffraction by an optical grating (which was well known) was generalised to three dimensions.

In most respects Laue's early papers lay down the lines for further investigations. Thus he developed the "Laue Equations" (one of the basic expressions of the behaviour of diffracted X-ray beams), and

carried out a tentative structure determination. Although in most respects this paper was correct, there was one major error -- he assumed that the diffracted rays consisted of characteristic radiation emitted by the atoms in the crystal on excitation by the incident ray¹.

2.3 The Work of the Braggs before World War I

British X-ray crystallography took the lead in structure determination in most areas after the First World War largely through the work of the Braggs, father and son. The list of achievements of the Braggs, and two other English workers (C.G. Darwin and H.G.J. Moseley) is truly amazing, for all work on X-ray diffraction was stopped at the outbreak of war at the end of 1914. W.L. Bragg wrote:

To sum up then the achievements of this first period from 1912 to 1920:

- (a) The wavelength of X-rays had been established.
- (b) A number of simple crystal had been analysed, including several with one parameter, and it had been shown that this parameter could be fixed with a high accuracy by comparing the order of the spectra. A parameter is a coordinate defining the position of an atom, which the crystal symmetry would permit to have any value.
- (c) A method for the accurate measurement of intensity had been found.
- (d) The Debye effect had been measured.
- (e) We had Darwin's formula for reflexion by perfect and mosaic crystals.
- (f) It had been realised that each crystal diffraction corresponds to a Fourier component of the density in the crystal.
- (g) Finally, a whole new range of crystalline substances had become available through the powder method, developed in 1916 by Debye and Scherrer in Switzerland and independently a year later by Hull in America. (W.L. Bragg: 1970a:172).

Bragg's list is not complete. For example, the discovery of the X-ray diffraction induced W.H. Bragg to abandon his theory of the corpuscular nature of X-rays, after it became clear that the diffraction effect

1. This account is derived from that of Ewald: 1962.

could much more easily be explained by a wave theory. In addition Bragg fails to note that he established "Bragg's Law" which, although similar to the Laue equations, treated the phenomenon of diffraction as a reflection rather than as a refraction. This formulation was the one normally used in the British tradition of X-ray crystallography. Further, Bragg mentions the measurement of intensities, but he does not mention the instrument that was developed by his father, the ionization spectrometer, which was used in this measurement. The ionization spectrometer was undoubtedly, in part, responsible for the development of quantitative X-ray crystallography in Britain.

Some work which was not of importance merely for X-ray crystallography, was also carried out. Thus W.H.-Bragg carried out work on emission lines and absorption spectra of various metals, measuring the relevant wavelengths accurately. Moseley, working independently, examined the characteristic X-ray beams of various metals, and determined their atomic numbers.

These years were felt to be ones of great opportunity -- W.L. Bragg describes the period as one when a prospector had discovered an alluvial gold field, and there were nuggets lying around just waiting to be picked up. X-ray crystallography was in no way separated from physics at this point. All the practitioners were either physicists or mathematicians, and the problems that were solved by the new technique were in many cases central to physics. At this time only W.L. Bragg was primarily interested in structure determination in its own right.

2.4 Postwar Work at the Royal Institution and Manchester

J.D. Bernal has written:

The position of the British schools in the history of the development of our subject is necessarily quite a special one.

Not only did Sir William and Sir Lawrence Bragg effectively start the study of crystalline structures by means of X-ray diffraction, but for many years their respective schools at the Royal Institution and in Manchester were the centres of world study in these fields. Naturally, important centres in other countries existed from the start ... but the primacy of the British schools was recognized, at the outset, by the large number of visits of young crystallographers, who were destined later to become the centres of schools of their own in other countries. Owing largely to the personal character of its founders the development of crystallography had, from the very outset, a peculiarly intimate and friendly character. All of those who worked at the Royal Institution or in Manchester carried away for the rest of their lives recollection of the atmosphere of active and exciting research which grew up around the Braggs, and the fact that they were father and son actually helped enormously to unify the whole subject. (Bernal: 1962a:374)

We shall base our lesson in this text. Not only were the Braggs and their pupils vitally important on a world scale but in addition they and their pupils virtually monopolised the development of X-ray crystallography in Britain. The number of persons who worked in the universities on X-ray diffraction between the wars, who were not fully, or largely trained by the Braggs and their pupils can almost be numbered on the fingers of one hand. Possibly the most eminent of the independent workers was Professor E.A. Owen, and among others were W.A. Wooster at Cambridge and H.M. Powell at Oxford. Otherwise it is possible to trace a direct intellectual ancestry back to the Braggs in every case. W.H. Bragg (who was at University College, London, from 1918 to 1923, and thereafter at the Royal Institution until his death in 1942), trained amongst many others, the following: J.D. Bernal; Dame Kathleen Lonsdale (nee Yardley); W.T. Astbury; J.M. Robertson; E.G. Cox; G. Shearer; A. Müller; and R.E. Gibbs. Several of these set up their own schools in the late 1920's and 1930's. J.D. Bernal moved to Cambridge in 1927, W.T. Astbury went to Leeds in 1928, and E.G. Cox went to Birmingham. W.L. Bragg, who was Professor of Physics at Manchester from 1918 to 1937, worked with and trained an equally

eminent series of workers: R.W. James; C.H. Bosanquet; A.J. Bradley; W.H. Taylor; J. Thewlis; J.T. Randell; C.A. Beevers; H. Lipson; and G.W. Brindley. This list is far from complete. Many of these went on in turn to found their own schools of X-ray crystallography: R.W. James at Capetown; H. Lipson at Manchester Technical College; C.A. Beevers at Edinburgh, and so on. The impression of the importance of these two centres is increased, as Bernal correctly notes, if the list of foreign workers is included.

For this reason it is possible to focus on the two main schools without missing any important developments in British X-ray crystallography up until about 1930. Thereafter, it is necessary to consider the work of some of the newly developing schools. This is particularly so in the case of proteins, where the main prewar work was done at three new centres -- at Leeds, under Astbury, at Cambridge under Bernal, and at Oxford, under Dorothy Hodgkin (nee Crowfoot) who was one of Bernal's pupils.

The key to the distinction between the two schools in the inter war period can be found in this quotation from Bernal:

From the very outset there was an almost tacitly agreed separation between the work of Sir William and Sir Lawrence Bragg, that is between the Royal Institution and Manchester, corresponding to that between organic and inorganic chemistry. With the one important exception of crystalline forms of silica, Sir William's laboratory occupied itself with organic crystals and Sir Lawrence's with mineral and metals. (Bernal: 1962a:376)

From the sense of the above passage, one can assume that Bernal means "explicitly" where he wrote "tacitly", for all the workers knew of the division. Dame Kathleen Lonsdale put it in the following way:

(This distinction) was a result, as we understood it, of a gentleman's agreement between W.H. and W.L. Bragg, that W.L. should do inorganic crystals and that W.H. should do the organic ones; ... they were each building up a school ... so that W.L.

Bragg went in for the silicates and metals, and those were the two sides of the Manchester school, while W.H. Bragg stuck to the organic and graphite, with the one exception that he had been working with Gibbs on the structure of quartz, and they went on working with quartz. But that was the only inorganic crystal that was being examined. Apart from that there were aromatic, aliphatic, and long chain compounds. (Lonsdale: 1970:3)

This meant that competition between the two schools was minimised.

It also led to a situation where, not unnaturally, the first protein crystallographers were recruited from the school of W.H. Bragg.

Only W.L. Bragg himself, of all the workers in his school, ever developed a major interest in the study of proteins.

2.5 The School of W.H. Bragg

The movement of personnel through W.H. Bragg's school and the spread of some of the workers in the universities, is depicted, in summary form, in Figure I. This chart, which takes the place of a discussion of the movement of workers, gives some indication of the power and influence of the school.¹

In as much as the work of the two groups laid the foundations of modern X-ray crystallography, any attempt to summarise those achievements will be inadequate. However, some of the main developments for which the Royal Institution school was mainly responsible, may be listed as follows:

(1) The development and exploitation of photographic and rotation methods of X-ray crystallography. The Bragg ionization spectrometer was exceedingly good at making accurate measurements of a small number of reflections. It was very slow and tedious, however, in measuring large numbers of reflections, and with the increasing complexity of crystals, the numbers of reflections that had to be measured increased. Thus photographic methods became more attractive as time went on, even

1. It should be compared with Figure 2 which gives similar data for the Manchester School of W.L. Bragg.

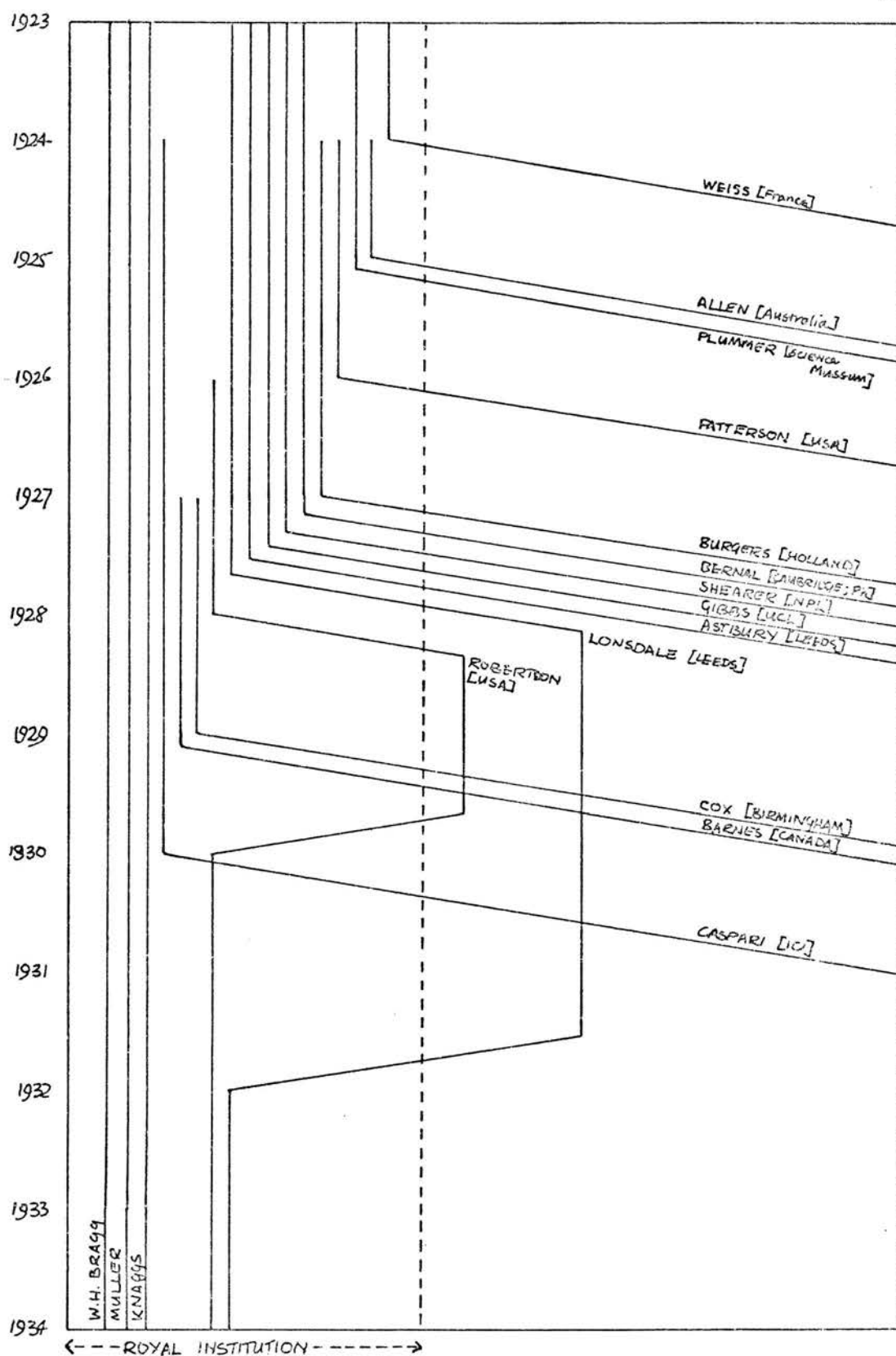


FIGURE 1
THE SCHOOL OF W.H. BRAGG

[This does not constitute an exhaustive list of all workers at the Royal Institution]

Source: Mainly from the Royal Institution, Davy-Faraday Laboratory Register of Workers, 1896-1932

though it was more difficult to measure intensities in this manner. Thus, by the middle twenties, it became clear that the future lay with photography, and in particular with rotation photography, where it was very easy to interpret the resultant photographs. This sort of development occupied much time for a number of the best workers -- notably Bernal and Astbury.

(2) The development of intensity measurements in photographic methods. This problem, which was of great importance, was tackled by Astbury, Cox and Shaw.

(3) The development of satisfactory X-ray tubes. Shearer and Müller were the most important workers in this line of development, but a number of others, such as Clay, also contributed. Müller developed an important innovation in 1928 when he built the first rotating target X-ray tube.

(4) The tabulation of the diffraction properties of the 230 space groups. This work, which was also carried out independently in Germany and the U.S.A., was published by Astbury and Lonsdale in 1924. This was an important step in the development of X-ray diffraction techniques since it made possible the close determination of space groups through fairly simple observation of the diffraction data.

(5) The development of the Fourier method, and its application to the determination of crystal structures. All early methods of crystal structure determination dependent on one of two factors -- either a trial-and-error solution, which could be checked against the diffraction data, or supplementary data, which would lead to a solution. In other words, the diffraction data were not quite sufficient, by themselves, to lead to an unambiguous answer in most cases. The extra piece of data required was the phase angles of the various diffracted beams.

The Fourier method of structure analysis offers a direct way of determining the structure, so long as the phase angles can be determined. Through the use of a Fourier series, it is possible to build up, from a series of wave forms of varying amplitude and phase, a function that corresponds to the periodicity of the refracting matter in the original crystal -- in other words the electron density. However, it was noted above that while amplitude may be directly measured, the phases may not. Since the phase angle is required for the full use of the Fourier method, various workers, and notably J.M. Robertson in the middle and late 1930's spent a lot of time developing another major innovation: (6) that of the isomorphous replacement technique. In essence this involves the comparison of X-ray diffraction photographs of crystal structures that are identical except in one respect. Usually the respect in which they differ is the presence or absence (or nature of) a heavy atom. By comparing the variations in amplitudes of the refracted beams in different cases the position of the heavy atoms may be determined, since they are likely to be relatively few per unit cell. Once the positions of the heavy atoms are known then the positions of the other atoms in the crystal structure can be calculated and the crystal structure solved.

The staff of the Royal Institution worked on both these methods. Lonsdale was one of the first to make full use of the Fourier method (on hexamethylbenzene ($C_6(CH_3)_6$) in 1929), although one-dimensional Fourier work was carried out by Shearer on ketones in 1925, and two-dimensional Fouriers were used by W.L. Bragg in the late 1920's. J.M. Robertson worked on a series of isomorphous molecules called the phthalocyanines, in the middle and late thirties, and developed the methods of isomorphous replacement to a new level.

The emphasis of this account has been on the methods developed at the Royal Institution, and it is perhaps in this area, where the workers in this school excelled. However, many notable structures were studied and solved during these years. In the very early days, after the First World War, various organic molecules were studied, although not solved. These included naphthalene, anthracene, and α - and β -naphthol. This work, which was mainly carried out by W.H. Bragg himself, did not result in structure solutions, but suggested that the discrete molecule of the organic chemists had some reality in crystal structures. Other work in the early years, included Astbury's on tartaric acid, R.E. Gibbs' on quartz, and W.G. Plummer's on C_6Cl_6 and C_6Br_6 . Lonsdale worked on succinic acid, and Müller and Shearer worked on long chain compounds.

One of the early successes of the new rotation method was published by Bernal in 1924 -- the structure of graphite; another, of fundamental importance to organic chemistry, was the structure of hexamethylbenzene, determined, as has been mentioned above, by Lonsdale. Many other lines of work were carried out however, which are less important, and do not warrant inclusion in an account of this length.

2.6 The School of W.L. Bragg

The movement of personnel through W.L. Bragg's school at Manchester is depicted in Figure 2. This school was also very influential, various of its members going to other departments in British and foreign universities. In addition a number of workers were taken by Bragg, first to the National Physical Laboratory, and then to the Cavendish Laboratory, Cambridge, when he moved to these in, respectively, 1937 and 1938. As in the case of the school of W.H. Bragg, this Figure

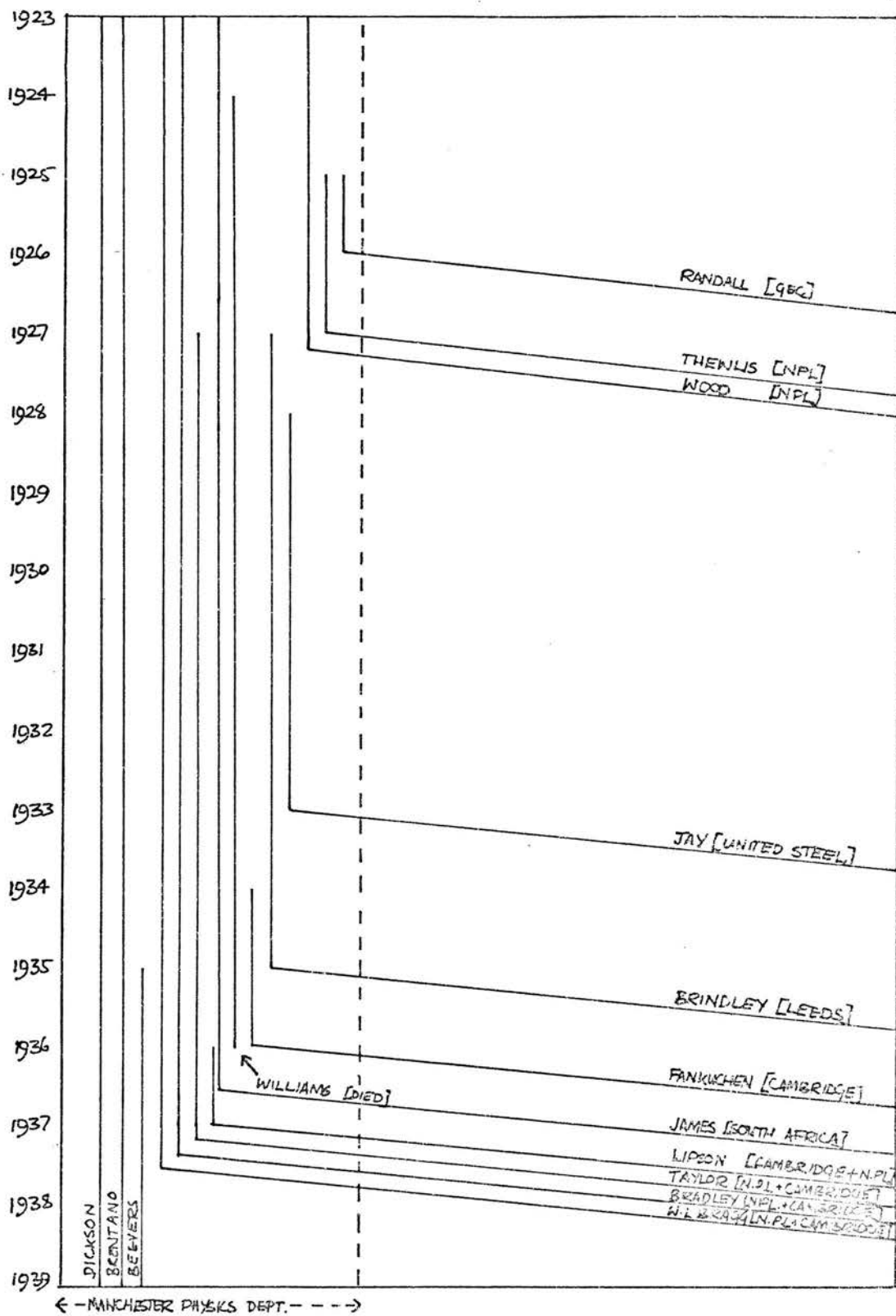


FIGURE 2

THE SCHOOL OF W.L. BRAGG

[This does not constitute an exhaustive list of all crystallographers at Manchester Physics Dept.]
 Sources: Various

takes the place of an exhaustive discussion of the movement of personnel through the school.

Research in the school was divided into two parts, particularly in the later years. One section worked on mineral structures and the structure of silicates in particular. The other section worked on metals and alloys and was headed by A.J. Bradley. Bragg held the two parts of the school together, for they used somewhat different techniques -- the mineral section concentrated on single crystal work, while the metallurgical section concentrated on powder work.

Work was also done in theoretical and methodological areas, and this will now be briefly summarised:

- (1) W.L. Bragg attempted to calculate characteristic atomic radii in 1921. Obviously, if radii could be assigned to different atoms, then the problems of crystal structure model building would be greatly simplified. Bragg's attempt was not successful as he made a wrong assumption in his calculation, and it was not until 1923 that the correct values were calculated by the Finnish crystallographer, Wasastjerna.
- (2) A major attack on the quantitative aspects of X-ray reflections was undertaken in the first instance by Bragg and James and led to a number of important results. Firstly, atoms were found to reflect X-rays with different degrees of efficiency at different angles. When this was compared with the theoretical scattering power of a single electron, it was calculated as the F curve. Secondly, through this work, absolute intensities of X-ray reflections could be measured.
- (3) Another aspect of the above work, was that the formulae for reflection of perfect and mosaic crystals (which had been devised by Darwin before the First World War) were tested for the first time, and the degree of "perfection" of the crystals was determined. This work, again had

implications for absolute measurement of reflections, as James wrote:

... ultimately a set of absolute F-curves for sodium and chlorine were obtained which were in fair agreement with what was to be expected from what was known at the time of the electron distribution in these atoms. (James: 1962a:423)

(4) This linked up with Hartree's important estimate of the F-curves that should arise from the Bohr atom. There was a discrepancy between the predicted and the observed curves, and it was not until a couple of years later when Schrödinger's wave theory of the atom was developed, and the calculations redone, that the predicted curves fell into line with those observed.

(5) James studied the F-curves of atoms, and their relationship to temperature. He, with Waller and Hartree, was able to show in 1928 that the Schrödinger model of the atom was plausible, by demonstrating experimentally that the atoms had half a quantum of energy at absolute zero.

(6) Bradley and Brentano worked on powder photography, the latter developing a camera which, unlike earlier models, could be used for accurate intensity measurements.

(7) The work of Bradley, and his colleagues, on the structure of metals, which will be briefly mentioned below, led to a re-evaluation of theories of metal structure, and was in part responsible for laying the foundations of modern metallurgy.

(8) The work of Bragg and his colleagues on the structure of the silicates, led to a general understanding of the structures of the silicates, which had previously been lacking. Thus, in the late twenties and early thirties, they were able to show that the structures of the silicates depends on the ratio of silicon atoms to oxygen atoms.

The Manchester school pushed methods of structure determination to a limit that had previously been unthought of. Many continental

workers were extremely skeptical about the work of the school, feeling that it was hopeless to try to determine the structures of substances with more than about a dozen parameters. Bragg himself wrote:

X-ray analysis acquired a far greater power. We used it to investigate the structure of minerals, in particular the silicates. They were initially only chosen as experimental material because they were moderately complex, and crystals were readily available from mineral collections. The unexpected result was that the survey cleared up in a remarkable way the whole system of mineral classification and put the structure of minerals on a rational basis. (Bragg, W.L. :1965b:167)

The work on the structure of metals was equally spectacular. Bragg wrote:

Bradley was a genius with the powder method, which he and A.H. Jay raised to a perfection of accuracy and analytical power which had probably never been equalled since. (Bragg, W.L. :1970b:175)

and, again, he noted:

In 1921 Westgren started his study of alloys in Sweden, and was the pioneer in this field. He was followed by Bradley, who had worked with Westgren and published the well-known structure of gamma-brass and α -manganese in 1926 and 1927. But it was in this 1930-40 period that Bradley and his school made their great contributions to the study of alloys and alloy phase-diagrams in a brilliant series of papers. The powder method was employed with a virtuosity which has perhaps never been excelled since, if indeed it has been equalled. Highly complex structures were analyzed. The knowledge so gained enabled Hume-Rothery's electron-atom ratio postulate to be interpreted by Jones in terms of Brillouin zones. Phase boundaries in binary and tertiary systems were accurately outlined. The order-disorder transformation was explored by Bradley and by Sykes. It received theoretical treatment by Dehlinger and by Williams and myself, and even proved to be so fascinating to the theorists that Bethe and Peierls were led into giving it their consideration. It is no exaggeration to say that the principles of metal chemistry for the first time began to emerge. (Bragg, W.L. :1961a:153)

2.7 British Schools of X-ray Crystallography 1919-1939

A brief social and intellectual sketch of the two main British schools has been offered above. From 1920 to at least 1930 these schools were not only the most important centres in Britain, but they were also among the most important international centres of X-ray

crystallography. This section will survey the relationship between the Braggs, and the other schools of crystallography that grew up in Britain in the inter-war period.

It has already been noted that it is not true to say that all X-ray crystallography in Britain originated either from Manchester, or from the Royal Institution. One very early worker in the field was E.A. Owen, who for many years undertook X-ray diffraction studies of metals at Bangor University. Other work, strongly related to X-ray crystallography, was carried out at other universities. Thus Barkla, whose name has already appeared in connection with the early dispute with W.H. Bragg over the nature of X-radiation, continued his work at Edinburgh on X-ray spectroscopy. His work on K- M- and L- levels of radiation was of the greatest importance.

One of the most interesting features of the developing X-ray crystallography was its relationship to classical morphological crystallography. Although some morphological crystallographers were suspicious of the activities of the X-ray crystallographers, the relationships between the two groups were excellent in both Oxford and Cambridge. Hutchinson at Cambridge was a particular friend of the X-ray crystallographers, although he never used the technique himself. He was in close touch with the Braggs after the First World War. In 1923 he became a lecturer in Mineralogy at Cambridge, and in 1926 he was made Professor. He sent Bernal to study under W.H. Bragg, and he also encouraged some of his own students, notably W.A. Wooster, to use X-ray crystallography.

Although Wooster was responsible for the introduction of X-ray crystallography to Cambridge, very shortly after his appointment as a demonstrator in 1927 Bernal came to Cambridge. He was appointed lecturer in structural crystallography. Crystallography occupied a

rather uneasy half way house between the Department of Mineralogy and the Cavendish in the late 1920's and early 1930's at Cambridge, and there was some ambivalence in university policy towards it, which may have been partly because Bernal was a well known left-wing figure. However, Bernal has noted that very few British universities developed a coherent policy towards crystallography, and Cambridge was the exception. Although the nature of the policy discussions that went on in the late twenties and early thirties is not clear, the upshot was that the Director of Research in Crystallography became answerable to the Cavendish Professor of Physics (Nature: 1935:405). At the same time X-ray crystallography was also done in the Department of Mineralogy and Petrology, so in practice two rather separate schools of X-ray crystallography grew up at Cambridge (although there was certainly contact between them).

Under J.D. Bernal, the work in the crystallographic section of the Cavendish Laboratory moved in the direction of biological molecules. In the early thirties Bernal worked on sterols and then he and his collaborators moved to the study of crystalline proteins, and viruses. W.A. Wooster's group worked mainly in crystal physics, and the development of techniques.

In 1937 various changes came to Cambridge. Rutherford died in that year, and W.L. Bragg, who had moved from Manchester to be Director of the National Physical Laboratory only a few months previously, was elected Cavendish Professor of Experimental Physics early in 1938. He brought with him several of his Manchester staff -- Bradley, Taylor and Lipson. Bragg's move to the National Physical Laboratory had vacated the Manchester Chair of Physics, and P.M.S. Blackett had been appointed to this position. Blackett had in turn moved from the

Professorship of Physics at Birkbeck College, London, and it was to this post that Bernal moved in late 1937. This round of Professorial chairs took, in all, less than a year to complete, yet it radically altered the situation for British crystallography. Firstly, crystallography was now firmly entrenched in the most famous and high prestige department in the country -- the Cavendish. It is clear that some were not entirely happy about this fact, as the nuclear physicists tended to look down on the X-ray crystallographers. The reaction of a number of staff and students on learning that Bragg was coming to the Cavendish was to say "how dull" (Wilkins :1971). Secondly, this was the end of the golden period of crystallography at Manchester, as Blackett took his own different research interests with him. Thirdly, it meant that the main focus of protein X-ray crystallography moved from Cambridge to Birkbeck (although it should be recalled that both Leeds and Oxford continued as important centres). Bernal took one of his collaborators, Fankuchen, with him to Birkbeck, and left only Perutz (who was very junior) to study proteins at Cambridge.

Cambridge was not the only university in which the classical crystallographers played a part in introducing X-ray crystallography. This also occurred at Oxford, although on a rather smaller scale. Bernal wrote of Oxford:

Unlike the other schools mentioned, where the initiative had primarily come from physicists, in Oxford the impetus for crystal studies was that of chemical crystallography originating with Myers and with Barker who had been a friend of Federov. X-ray studies began with the appointment in 1929 of Mr. H.M. Powell as demonstrator of chemical crystallography. (Bernal :1962a:381)

Powell who was a student of Barker's was encouraged by the latter to learn the technique of X-ray crystallography. The second product of the Oxford school, whom Bernal described somewhat inaccurately as

Powell's student, was Dorothy Crowfoot (later Hodgkin). Crowfoot attended a wide range of undergraduate courses, and she sat in on the course on crystallography given by Barker, although she did not take the exam. (Hodgkin :1970a). She went to work under Bernal almost by accident, in 1932, and it was here that she obtained her main training in X-ray crystallography. In 1934 she returned to Oxford, where she developed her work in various biological molecules.

All the important schools of X-ray crystallography that grew up in the inter-war years that had origins independent of the Manchester - Royal Institution axis have now been mentioned. Even in the case of several of these, pupils of the Braggs came to play an important part. In several other cases pupils moved out from the two main schools, and founded their own research groups. Possibly the most important of these from the point of view of protein X-ray crystallography was that of W.T. Astbury at Leeds, who took a post as Lecturer in Textile Physics at the Textile Industries Department in 1928. This department, and Astbury's work will be considered in more detail in the next section.

Bernal and Astbury were not the only workers to leave the Royal Institution in the late 1920's. Lonsdale went to the Physics Department at the University of Leeds, although her work was still closely connected with the Royal Institution. She was in Leeds for five years in all, although during much of that time she was having a family rather than working full time. When her husband obtained a job in the London area, she returned to the Royal Institution. It was during the Leeds years that she determined the structure of hexamethylbenzene. When she returned to the Royal Institution she moved from X-ray crystallography to the study of paramagnetism in

organic crystals.

Cox left the Royal Institution to go to Birmingham in 1929, where he started a vigorous tradition of organic X-ray crystallography. Bernal has described this group as "one of the most fertile centres of X-ray analysis". Among others that moved out, and continued work on X-ray crystallography, were Gibbs, who went to University College, London, and Shearer, who went to the National Physical Laboratory. Much later, in 1942, J.M. Robertson accepted the Chair of Chemistry at Glasgow.

Very nearly all of the crystallographic schools in British Universities in the 1920's and 1930's have now been covered. One or two small groups, centred round other individuals remain to be mentioned. Thus, G.W. Brindley, one of the workers from W.L. Bragg's school at Manchester moved in 1935 from Manchester to the Chemistry Department of the University of Leeds. There was a small group at Bristol, under Piper, in the late twenties and early thirties, which worked on fatty acids and waxes. C.A. Beevers and H. Lipson started work on X-ray diffraction at the Liverpool Physics Department in 1934, and developed the rapid method of calculating Fourier functions known as the "Beevers-Lipson strips". After solving the structure of copper sulphate, they moved in 1936 to join the group at Manchester, thus physically joining the school of which they had been de facto members.

One of the general features that comes out of the above survey is the fact that crystallography grew in a haphazard way in Britain. Thus Bernal has written:

When we look at the actual lines of development, we see very clearly that they depended on the possibilities available to the original founder, to get the necessary support and interest in his work. Those who were successful in achieving

the professorial chair in a fairly large university were able to set up large schools which proliferated into many other places. Those, on the other hand, who occupied relatively subordinate positions in physics or chemistry departments, remained for the most part, as isolated research workers or having one or two students at a time, and though the work they did was of the highest quality, it can hardly be said that they founded a school. This is brought out very clearly also by the way in which the transfer of an individual research worker from one university to another could result not only in the setting up of a new school in the second university, but often in the disappearance of crystallography altogether from the first. What we see, accordingly, is a fluctuating pattern lit up for a few years by the presence of a research director with drive for the time of his tenure there.
(Bernal:1962a:376)

Manchester and the Royal Institution rate as stable schools. At a later date, Leeds, Cambridge, Birmingham, Glasgow and Oxford came to be important and stable centres. But the study of X-ray crystallography virtually stopped at Manchester after 1937, and it went into a decline at the Royal Institution after the death of W.H. Bragg in 1942 (although with wartime conditions the amount of work and number of personnel had already suffered great reductions).

Bernal has also written:

One conclusion is very evident, namely, that the development of this subject was a matter in which general or conscious planning had extraordinarily little to do. Only in one or two cases, notably in Cambridge, did the University, itself, decide that it must have a crystallographic department, but in most cases, crystallography occurred almost unintentionally when a Chair of Physics or Chemistry happened to be awarded to a crystallographer as the most distinguished available candidate in a field which covered all branches of the subject. The non-establishment of chairs of crystallography in Great Britain has prevented the continuity which could so easily have been ensured in view of the availability of men of quite exceptional enterprise. There is no doubt that crystallography at several stages in its development in Britain was such an attractive subject that it automatically selected such people and the fact that a relatively unknown subject could acquire, in such a short time, no less than seven Fellows of the Royal Society, is some indication of it.
(Bernal :1962a:377)

Bernal raises four main points here. Firstly, there is the fact that there was little planning of crystallography in British Universities. Secondly, there is the fact that crystallographers were obliged to compete for positions, not only with each other, but also with far wider groups coming from physics, chemistry, or in some cases mineralogy, textile studies, etc. Thirdly, there is the fact that crystallography was a very attractive subject at certain times. Fourthly, there is the proposition that crystallographers managed, none the less, to gain ~~very~~ high prestige, as is evinced by the fact that quite large numbers of them became Fellows of the Royal Society.

Looking into this in a little more detail, if Figure 3 entitled Types of Departments in British Universities in which X-ray Crystallographers Held Posts 1920-1950 is considered, it will be seen that the proportion of X-ray crystallographers holding posts in chemistry departments increased considerably after the war, and the proportion (though not the absolute numbers) in physics departments decreased. This seems to be a reflection of the increasing acceptance by chemists of those with a major training in X-ray crystallography.

It seems that X-ray crystallography after the early 1920's began to be centred on problems that were less of interest to a great many physicists, while becoming increasingly concerned with problems that were of interest to other groups -- especially chemists, mineralogists, and metallurgists. Although there was undoubtedly some resistance from some quarters, other chemists expressed great interest in the new technique. While X-ray crystallographers, such as the Braggs remained in very high positions, this ensured that younger crystallographers were able to obtain positions in their physics departments. But the nature of the changing interests of

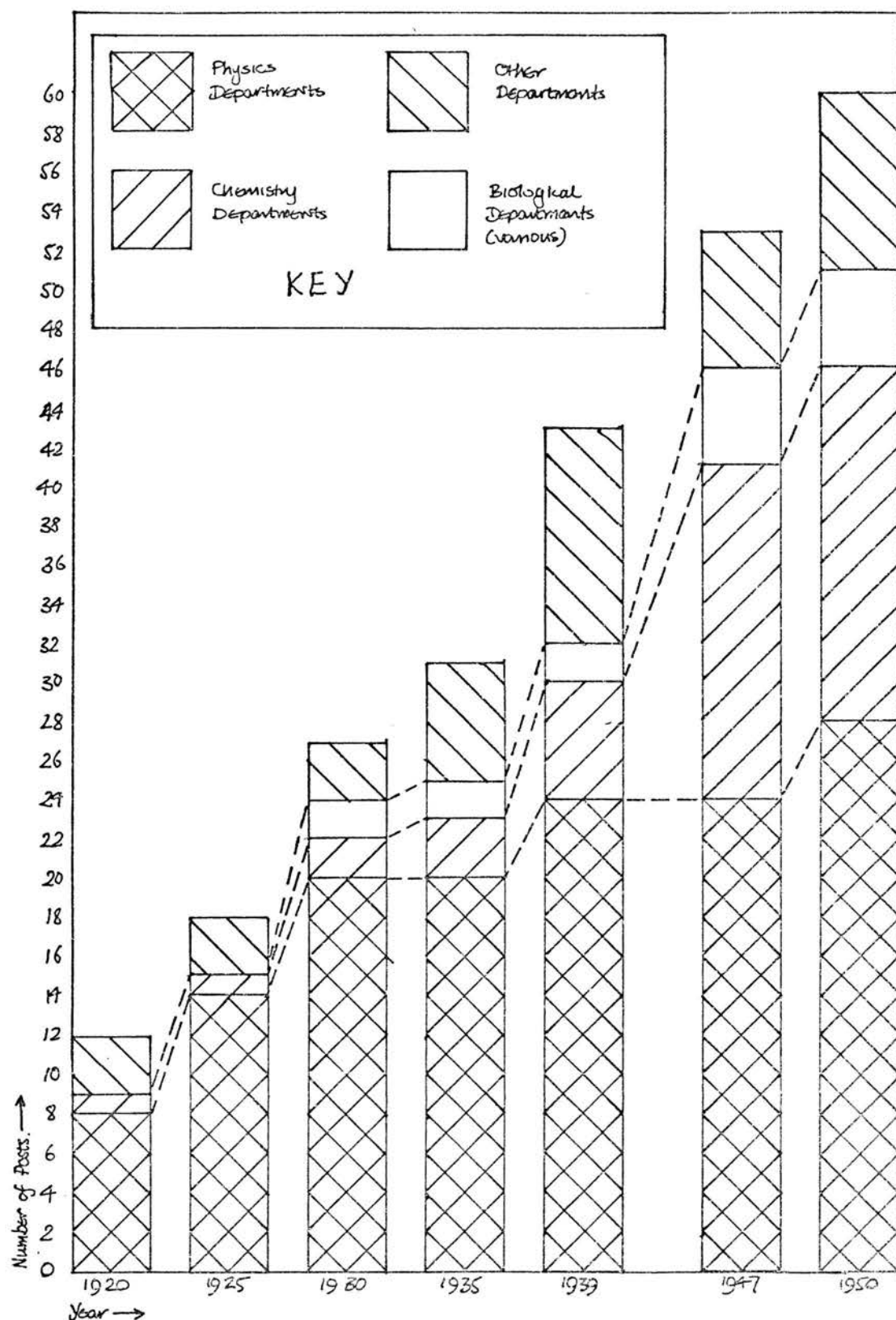


FIGURE 3 TYPES OF DEPARTMENTS IN BRITISH UNIVERSITIES IN WHICH X-RAY CRYSTALLOGRAPHERS HELD POSTS, 1920-1950 (EXCLUDING POSTS HELD AT ROYAL INSTITUTION)

other physicists and chemists meant that without this influence crystallographers were increasingly likely to come from and obtain posts in chemistry.

Bernal was certainly correct to suggest that there was little or no conscious planning of crystallography in the British Universities. Departments of crystallography were not set up and on the whole, as has been pointed out, crystallographers were obliged to compete for positions with a wide range of other specialists. Despite Bernal's remarks, it is difficult to determine how attractive crystallography was at different times, although Bernal suggests that it was, at times, very attractive.

If election to the Royal Society is some indication of general status in the scientific community, then 23 Fellows have been, first or foremost, crystallographers. (See Figure 4 entitled X-ray Crystallographers and the Royal Society.) It is difficult to distinguish rigorously between crystallographers and non crystallographers, but so far as possible, only scientists elected primarily for their contribution to X-ray crystallography have been included in this chart (with the exception of W.H. Bragg, who was elected before 1912).

This figure also gives further indication of the importance of the two Braggs in the development of crystallography in Britain. Of all 23 Fellows, only three are completely independent from the Braggs. The largest number constitute, by any reasonable definition, pupils of the Braggs, or pupil's pupils. No less than five of the young members of W.H. Bragg's Royal Institution school finally became Fellows -- Astbury, Bernal, Cox, Lonsdale and Robertson; and Bradley, Randall, James, and Lipson, who were members of the Manchester School, also became Fellows.

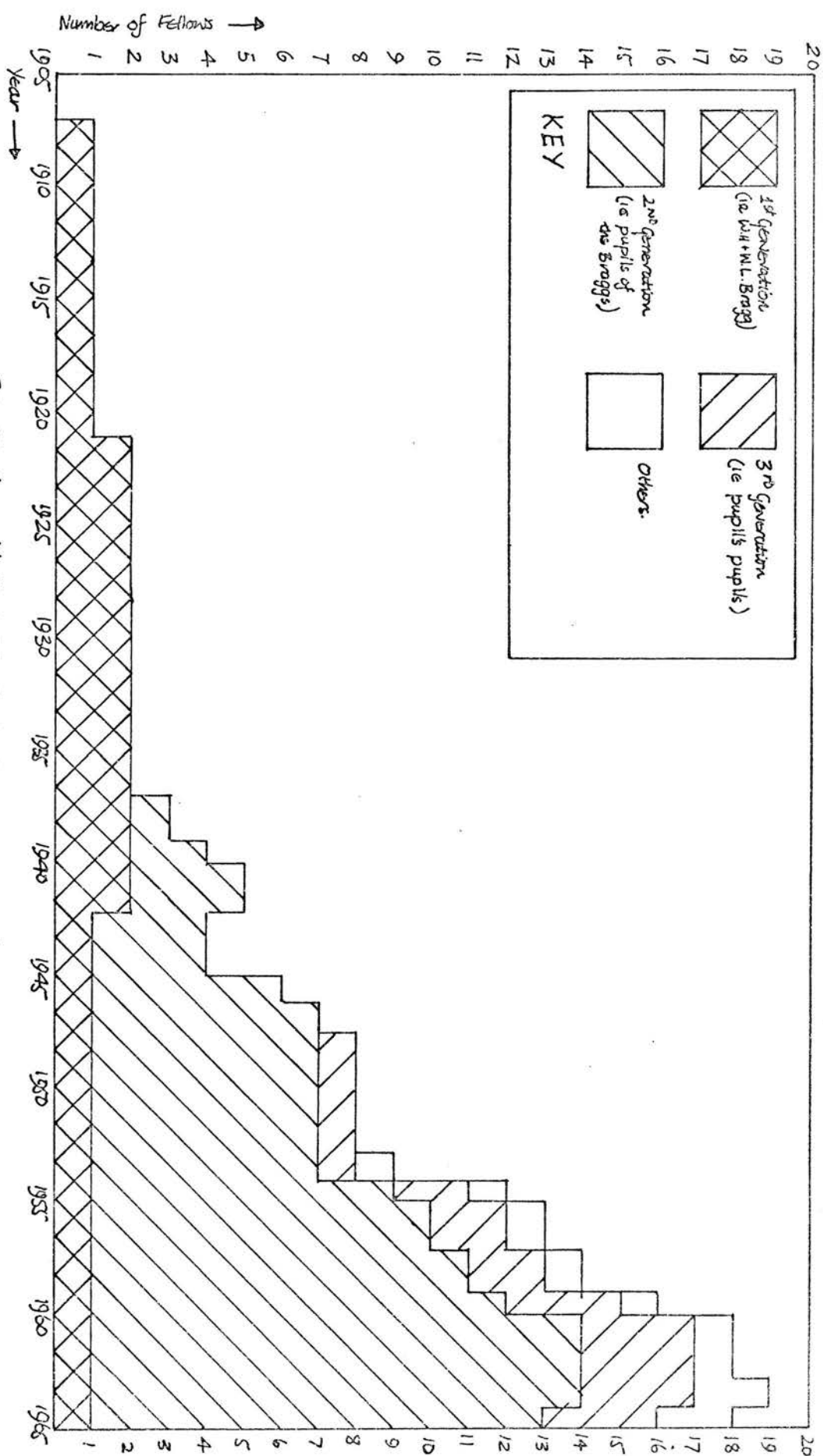


FIGURE 4 X-RAY CRYSTALLOGRAPHERS AND THE ROYAL SOCIETY

This section has attempted a brief review of the early growth of X-ray crystallography in Britain. It has mentioned the institutional growth of the specialty, emphasising the importance of the Braggs and their pupils. It has outlined some of the main developments in crystallographic techniques, and some of the most important crystals, or crystal types structured. It is, however, no more than a summary prelude to the more detailed discussion of British Protein X-ray crystallography which follows.

3 THE DEVELOPMENT OF PROTEIN WORK: ORGANISATIONAL SETTING

Protein crystallography has been carried out at the following British centres only:

Leeds:	1928-	Astbury and co-workers
Cambridge:		
	1928-1937	Bernal, Hodgkin, Perutz, Fankuchen
	1937-1946	Perutz
	1946-1954	Bragg, Perutz, Kendrew and Crick
	1954-	Perutz, Kendrew, Crick and co-workers
London: Birkbeck		
	1937-1939	Bernal, and Fankuchen
	1945-	Bernal and Carlisle
London: Royal Institution		
	1954-	Bragg, Phillips and co-workers
Oxford:		
	1934-1965	Hodgkin and co-workers
	1965-	Hodgkin, Phillips and co-workers

This section describes the relevant parts of the careers of the important workers named above, primarily in organisational terms, as a background to the detailed study of the scientific work.

3.1 Summary

The number of centres of protein crystallography in Britain has been very limited in number. They may all be traced, directly or indirectly, from the influence of W.H. Bragg at the Royal Institution. Two of Bragg's pupils, W.T. Astbury and J.D. Bernal were the leading

protein workers in the 1930's. In the 1940's the most important work was done by Perutz, Kendrew and W.L.Bragg at Cambridge, by Bernal and his student Carlisle, at Birkbeck College, London, by Dorothy Hodgkin at Oxford, and by Astbury and his pupils at Leeds. In the 1950's Perutz, Kendrew, Bragg and Crick developed successful methods of protein structure determination. In the middle fifties, Bragg retired from the Cavendish and started another group at the Royal Institution with the help of Kendrew. Phillips carried out much of his successful protein structure analysis in this group.

The purpose of this chapter is to outline this organisational development in a little more detail. The advances in techniques and understanding will be more fully discussed in later chapters, but inevitably there is no clear distinction, and sections of this account will cover episodes that more properly belong in those chapters.

3.2 Astbury and Leeds

No important protein X-ray crystallography was carried out in Britain before 1926. In that year W.H.Bragg at the Royal Institution became interested in the work of Meyer, Mark, Polanyi and others, on the structure of cellulose and other biological fibres, including silk. Bragg was responsible for the presentation of semi-popular lectures at the Royal Institution, and prompted in part by the German work, he decided to talk on "The Imperfect Crystallisation of Common Things". Bernal has written of the lectures:

One of Sir William Bragg's most subtle ways of directing research -- because less of a Director you could hardly imagine -- was casually to ask one of the research workers to help him in preparing some photographs or material for

a lecture. We did not like this too much, actually, at the Davy-Faraday because it took time off our work and, in fact, the preparation of the children's lectures occupied the whole of the autumn term. Nevertheless, though we did not know it, it often proved the most valuable and instructive part of our research training. (Bernal :1963a:6)

On this occasion, Kathleen Lonsdale reports:

He asked W.T. Astbury to assist him in the preparation of this lecture by taking X-ray photographs of natural fibres, such as were being taken (in Germany). This Astbury did with such thoroughness that he became interested in the field (Lonsdale :1962b:412)

Indeed, he became so interested that from this time onwards he concentrated almost exclusively on the structures of proteins, and in particular on the structure of keratin.

Astbury carried out most of his work in the Department of Textile Industries at the University of Leeds. He was appointed in 1928 as Lecturer in Textile Physics. The Department of Textile Industries was interdisciplinary in nature, with workers from a number of different backgrounds, the most important of these being protein chemistry. The most influential person in the Department for Astbury in the early years was J.B. Speakman, who had been appointed Lecturer in Textile Chemistry in 1924. Speakman had already done a little work on the X-ray diffraction of wool, but with little success.

Astbury wrote of his move to Leeds:

As an adjunct to Speakman's physico-chemical investigations on the wool fibre commenced in 1926, the University of Leeds asked Sir William whether he could supply someone to carry out complementary investigations in textile physics. I wanted to stay on at the Davy-Faraday, of course, but I accepted the post of Lecturer in Textile Physics in 1928 and set about building up a Textile Physics Research Laboratory based chiefly, in the first place, on X-ray diffraction studies of wool. (Astbury, quoted in Bernal :1963a:7)

When he moved in 1928, resources available were not large:

H.J. Woods was appointed Research Assistant, and I had two Ph.D. students and an apparatus allowance of £150 p.a.;

otherwise the room provided was quite bare and all we knew was that certain clothes were made of wool, and that wool in turn was composed of an "amphoteric colloid" called keratin -- a biochemically lifeless and uninteresting protein which was some kind of polypeptide. Except for a Hyvac pump we constructed all our own apparatus For over 15 years from the early 30's our work was supported principally by the Rockefeller Foundation (Astbury quoted in Bernal :1963a:7)

Indeed, the Rockefeller Foundation were very helpful. Starting with a relatively small grant of \$1,800 in 1934 they made grants totalling about \$180,000 between 1934 and 1947 (Rockefeller :1970). Bernal suggests that Astbury supported some of his research assistants from money raised by the International Wool Secretariat.

Occupying a position in this rather unusual department, which had interests that verged on the applied, Astbury made contact not only with a wide range of scientists, but also with practical men and technologists. He was always a little pessimistic about the attitude of the wool industry to his work. Professor Whewell has written:

(Astbury) certainly did from time to time feel that the work that he and his colleagues were doing was not fully appreciate (sic) or understood by the wool industry. This is only partly true, as is evident from his book "The Fundamentals of Fibre Structure", where he set out his views for the benefit of the practical textile men.

In my view, Astbury's pessimism, which incidentally is shared by almost every applied scientist for whatever industry he is working, does not indicate the real situation. He was in fact a member of the post-war Working Party and this, in itself, indicated that the industry was willing to listen to what scientists had to say. They did not, of course, always act upon his advice, but this is, perhaps, not to be expected. He was held in very high regard by many members of the industry and the novel points of view which he put forward had a great influence on thinking in the wool textile industry, particularly by those members who were concerned with research and development. (Whewell :1971:2)

Astbury's department was always rather small. This was partly because of financial difficulties, but it was also a function of Astbury's

personality. Bernal wrote that:

Part of his difficulties stemmed from his innate or traditional extreme independence. He really belonged to the great sealing-wax and string tradition. I competed with him in an application for a post in Cambridge in 1927 and when he was asked in the interview by two eminent scientists of the time what his view was on collaboration, he answered very rudely: 'I am not prepared to be anybody's lackey' -- and he never was. In that sense Leeds gave him an ideal job. No one told him what to do, no one could tell him what to do. And, conversely, he did no empire building. He was in his own way too proud to seek for influence or many colleagues. Nevertheless, he was an extremely social and co-operative person but it was a free co-operation and he did not fit into any organization. Consequently his highly original and personal research ideas never secured the support they deserved. (Bernal :1963a:26)

An unknown colleague of Astbury's wrote:

He had the capacity to hold together a comparatively small team for so long with very little material inducement. To us "the lab" was an organic whole; Astbury was, of course, our inspiration and we were content to let him be our mouthpiece, but every paper which was published, no matter whose name was on it, was felt to be in a large degree a corporate achievement. (Bernal :1963a:29)

Thus there were relatively few collaborators. There were Bell, Woods, Lomax, Street, Marwick, Atkin, Preston, Dickinson, Bailey, Rudall, MacArthur, Spark and Reed. These are the more important whose names appear as co-authors in Astbury's bibliography. Bernal wrote:

Perhaps the man who had the greatest influence on Astbury at the outset of his career was Dr. Speakman, an imaginative textile chemist who was initially responsible for interesting Astbury in the physical properties of materials which was to be one of the major channels of discovery of the nature of the polypeptide fold. It seems to have been an ideal collaboration. Of his other collaborators, MacArthur was longest associated with him but MacArthur had a temperament very different from Astbury, critical where Astbury was intuitive, refusing to be led along the paths which Astbury's genius often indicated or into the traps into which he so often fell. He got on better with the biological colleagues, with Rudall, Preston and Bailey. Some of his most interesting work was done with the physiologist Dr. Sylvia Dickinson, also with a character very complementary to his, extremely self-critical. The traits in his character that were to be most harmful to him were his lively scientific imagination and his rashness and lack of self-criticism. (Bernal :1963a:27)

He was made a Reader in 1937, and in 1945 he was made Professor of Biomolecular Structure. He wrote of this:

After the war, the biological implications of our work having long outgrown the merely textile, the University inaugurated the present Department of Biomolecular Structure and appointed me to the Chair. (The title I wanted was "Molecular Biology", the name I myself had first propagated, but the committee thought it was asking too much to describe me as any sort of biologist). (Astbury, quoted in Bernal :1963a:7)

Bernal wrote:

Astbury certainly had to start research the hard way but actually he had to keep it up the hard way for the rest of his thirty-three years at Leeds. The Rockefeller grants only enabled him to buy a little apparatus and pay the salaries of a few additional research workers. They could do nothing to help him with building, nor could the University. To the very end, after he had acquired an international reputation and many honours, Astbury's new Laboratory of Biomolecular Structure was really the rooms of an old house acquired by the University and in every way unsuitable for the work he had to do. Like many others of us, he never, in the course of a long scientific life, had a new building made for him for the purpose of research. Nevertheless, in view of his temperament, this did not dishearten him, although in his latter years I know he felt it acutely as an index of the lack of value that was put on science in this country. (Bernal :1963a:8)

So the initial picture of Astbury and his group is of a small number of dedicated workers from different backgrounds ++ Bernal mentions biologists, biochemists, and specifically a physiologist. Astbury was in a very dominant position -- the "mouthpiece" of the group. Organisationally he advanced to a Readership, and then to a Chair, in a new, interdisciplinary area. In terms of honours, Astbury was elected a Fellow of the Royal Society in 1940, and he was Croonian Lecturer in 1945. In terms of support and facilities, he never received overmuch. His laboratory, which was so important for the advancement of protein studies in the 1930's, if not the 1940's and 1950's depended on grants from such bodies as the Rockefeller Foundation.

3.3 Bernal, Cambridge and London

3.31 Cambridge

Although Astbury was first in the field of protein studies in Britain, one of his former colleagues at the Royal Institution, J.D. Bernal, also developed an early interest in the area. Bernal, like Astbury did some brilliant work at the Royal Institution in the middle 1920's. After his move to Cambridge he developed the Crystallographic Laboratory until it became one of the most important centres of X-ray crystallography in the country. No account of the Cambridge group would be complete without a brief mention of Bernal's character. C. P. Snow has written:

People have sometimes asked, just how will he rank in scientific history in the narrow sense. I think the answer is that in natural gifts he stands very high; he is the most learned scientist of his time, perhaps the last of whom it will be said, with meaning, that he knew science; he has enormous imaginative sweep and deep insight; he has a major scientific purpose. And yet his achievement, though massive, will not dominate the record as it might have done. This is partly owing to a peculiarity of his nature. He likes to start something, drop an idea, get the first foot in -- and then leave it for someone else to produce the final finished work. The number of scientific papers, all over the world, published under other names, which owe their origin to Bernal is very large. But he has suffered from a certain lack of the obsessiveness which most scientists possess and which makes them want to carry out a piece of creative work to the end. If Bernal had possessed such obsessiveness he would have polished off a great deal of modern molecular biology and won Nobel Prizes several times over. (Snow :1966:26)

Bernal's original appointment at Cambridge was as Lecturer in Structural Crystallography in the Department of Mineralogy.

(Nature :1927:317) As was mentioned in the last chapter, there were discussions going on at Cambridge at the time about how crystallography should be organised, and in the early thirties Bernal found himself as head of the Crystallographic Laboratory, which was a subdepartment in the Cavendish and ultimately under the control of

Rutherford. Crystallography was rather a low status branch of physics:

X-ray analysis of crystalline proteins and viruses was begun at the Cavendish Laboratory by J.D. Bernal in the middle thirties, some years before Bragg arrived there. Bernal headed the Crystallographic Laboratory, a sub-department housed in a few ill-lit and dirty rooms on the ground floor of a stark, dilapidated grey brick building. These dingy quarters were turned into a fairy castle by Bernal's brilliance and his boundless optimism about the powers of the X-ray method. He would occasionally tell Lord Rutherford, the Cavendish Professor of Physics, of his first crystallographic expeditions into the fields of biology, but no echoes of these encounters reached us students. We were but a side show among the glittering spectacle of atomic physics that unfolded itself in other parts of the Cavendish Laboratory. (Perutz :1970a:183)

The Crystallographic Laboratory was not especially large. Bernal had rather few students, and even fewer worked in the area of protein structure. The most important of these was Dorothy Crowfoot who worked with Bernal between 1932 and 1934. Another important student, who came from America via the Manchester School of W.L. Bragg, was I. Fankuchen. Fankuchen worked with Bernal from 1936 till 1939, when he returned hurriedly to the U.S.A. on the outbreak of war. In 1937 Bernal moved from Cambridge to London, and became Professor of Physics at the London College of Birkbeck.

Bernal was by no means exclusively interested in the proteins. He did work on other biological molecules -- the sterols and viruses -- both before and after the Second World War, on metals (in the early thirties) and on the structure of liquids (a subject that has been of continuing interest to him.) Hodgkin recently remarked:

The idea about having only one interest is mistaken. I think that scientists have a great many interests, and the theoretical problems in one field turn up in another. Bernal had worked on graphite, of course, which is a sort of half-way house between organic chemistry and metals, and he went off in both directions at the same time. (Hodgkin :1970a:2)

His interests were not restricted to crystallography. He was active in both left wing politics and the history of science. Both his scientific and social life was hectic, and sometimes disorganised. The following extended quotation from an interview with J.M. Robertson gives the flavour of Bernal's life-style. It concerns Bernal's inaugural lecture at Birkbeck in 1937 or 1938:

Fankuchen used to try to organise Bernal in those days.

Anyway, for his inaugural Bernal hadn't prepared anything in advance, which was as always, but it didn't matter because he was going to prepare it on the day. Then at 10.00 am. Langmuir (a strong supporter of Wrinch's cyclol hypothesis of protein structure J.L.) turned up and went into Bernal's office at Birkbeck, and, of course, everyone knew what they were arguing about. Anyway, Langmuir stayed with Bernal until about 5.00 pm., ~~when he left~~. Then Fankuchen grabbed Bernal and they got in a taxi, and they came round to me at the Royal Institution. Bernal needed some lantern slides for his lecture, which was to be held at 6.30 pm., and I was the first person who occurred to them. So we went through all my slides, and they took some out, and then he decided that he didn't have enough, so we went downstairs, and we went through W.H. Bragg's cupboards to get some more -- he had some slides, most of which I had taken. Then Fankuchen pushed Bernal into the taxi, and they rushed off.

Bernal had to go to a sherry party with all the important people beforehand, so he left Fankuchen with all the lecture slides. Unfortunately "Fan" had absolutely no idea what order Bernal wanted them in, and indeed, Bernal himself didn't know either. So Fankuchen just had to give them all to the projectionist in random order. When Bernal gave the lecture he just called for the slides, and as they came up he saw what they were, and talked about them quite impromptu. I didn't go to the lecture -- I'd had enough of them by then -- but those who did go said that it was the best lecture Bernal ever gave! (Robertson :1970:7)

This improbable story is corroborated in all important details by Dorothy Hodgkin in a recent lecture. (Hodgkin :1969a:3)

3.32 Birkbeck

Bernal was responsible for a number of important breakthroughs in the early 1930's. He and Crowfoot took the first good X-ray

diffraction photographs of crystalline proteins. However, although he organised a major project on protein X-ray crystallography after the Second World War, he did not contribute notably in this field after the thirties. Much of his energy was spent in the pursuit of political causes, but this was not the only reason. Did the other interests distract from his scientific work? Hodgkin has noted:

Bernal did spend quite a lot of time on scientific work. I think that you have to remember that very few people are full time scientists in the real sense, so that I think that particularly during the early period he spent quite a lot of time on scientific work. It was during that early period that most of the more serious observations were made, and the various trains of thought and work started. If it had not been for the war he would probably have followed them through much more fully himself. Of course, the war meant a change of occupation. In his conduct of the war research he had many people working with him, and he was able to give orders -- "Do this!" and "Do that!". The war made him into much more of an administrative scientist, and much less of a bench scientist. And, as was the case with a great many other people, this affected him after the war. He tended to have research students working for him. But even so, he still spent a great deal of time on the water theory, and it would have been quite wrong to regard him as not an actively working scientist. (Hodgkin :1970a:4)

During the war Bernal continued to spread his interest in proteins.

Kendrew had long conversations with Bernal and Waddington -- especially Bernal -- and he became convinced that the structure of proteins was an important problem. For a time he thought that he might work with Bernal, but things turned out differently, and he joined Perutz in Cambridge¹.

Bernal returned to the study of proteins in 1945 in a somewhat chastened mood. The reasons for this will be considered in detail elsewhere, but essentially it was because he realised that proteins were

1. This information is taken from an interview with John Kendrew; Kendrew :1970a:1.

very much more complicated than had been expected (or perhaps hoped) in the 1930's. In 1945 he advocated a very long term approach. He wished to mount major projects on both problems of instrumentation -- the production and detection of X-rays -- and on problems of calculation. Support for this project came from the Nuffield Foundation, which made available 25,000 between the years 1945 and 1950, in order to finance a centre of biomolecular research at Birkbeck. The project had three sections. One on X-ray analysis was directed by C.H. Carlisle. Carlisle had been one of Bernal's students although he had worked in Oxford for much of the war. When he came to Birkbeck he worked on the enzyme, ribonuclease. The second section was concerned with electronic techniques, and in particular with the development of a fine focus X-ray tube. This was headed by W. Ehrenberg, a physicist who had worked with Polanyi in Germany in the 1920's. The third section, which was headed by A.D. Booth, was concerned with the development of automatic methods of computation¹.

Like Astbury, Bernal had to make use of old buildings. Such was the housing problem in London immediately after the war, that it was impossible to find decent accommodation at all. The only space available was in two bombed-out houses in Torrington Square. There were no windows, and there was no source of heating. All the power had been turned off, and there were not even floors in some of the rooms. By 1948 the houses were sufficiently well converted to warrant an official opening, which was carried out by Sir Lawrence Bragg in July of that year. (Birkbeck :1948)

1. Most of this information, and that which follows comes from a Nuffield Foundation Report. Nuffield :1954:105ff, and from an interview with W. Ehrenberg. Ehrenberg :1970.

In 1949 the first regular postgraduate course in crystallography was set up, and in the same year the Nuffield Foundation grant ran out. It was decided that:

as the Foundation was then embarking on a programme of increased support for biological studies, to which Professor Bernal's work is a valuable contribution from the physical side, a further grant of £32,000 for the three years 1949-52 was made, timed to terminate at the beginning of the new university quinquennium. (Nuffield :1954:105)

Although the progress made at Birkbeck was rather disappointing, Bernal's laboratory none the less acted as a centre for many of those interested in proteins. Furberg, came to work in the laboratory in 1947 on the ribose nucleoside and the nucleotide of cytosine. In 1953, Franklin, who had worked at Kings College, London, with Wilkins, came to Birkbeck, and worked on the structure of tobacco mosaic virus.

Why was the group so unsuccessful in its attempt to structure proteins? Ehrenberg's explanation is as follows. He himself, together with another worker, developed a fine focus camera which was quite successful. Booth, although he produced a calculating machine of sorts, did not seem to have the knowledge or drive to develop a successful computer. Carlisle, who tended to work in some degree of isolation with only a couple of research assistants, also suffered from a lack of drive. He felt that Booth should hand him a computer on a plate, and he did not encourage and push the latter when this might have been worthwhile. Bernal was somewhat remote from the laboratory, and was deeply engaged in other projects (including writing his book Science in History), so his energy and vision were lacking. Carlisle, unlike Bernal, was probably not aware of the size of the computing problem in protein structure determination. Ehrenberg therefore suggested that one of the main drawbacks of the Birkbeck

group was that they did not form themselves into a team.

Perhaps as a result of this the group was not in close touch with workers at other centres. Their only regular contact was with Dorothy Hodgkin, who came to the laboratory fairly frequently. There was no useful contact with the workers at Cambridge, and it seems from the remarks of a number of workers (notably Phillips :1970; Beevers :1971) that Carlisle was widely regarded as incompetent. This would help to explain the isolation and lack of success of the Birkbeck group.¹

The difficulties should not be over-emphasised. The work done by Furberg was very important in the final solution of the structure of DNA. The work done by Franklin and her collaborators on tobacco mosaic virus was also very important.²

3.33 Summary

Looking at Bernal's career we see the following. Having done an undergraduate degree, mainly in Physics, at Emmanuel College, Cambridge, he went to work with W.H. Bragg at University College, London, and at the Royal Institution. From there he became a lecturer in crystallography at Cambridge, and in 1934, Assistant Director of Research. In 1937 he moved to become Professor of Physics at Birkbeck College, where he remained for over thirty years. In 1937 he was elected a Fellow of the Royal Society.

In the early days Bernal's laboratory was small. He had few students -- the most important being Dorothy Hodgkin, Max Perutz, and

1.¹ Although Carlisle developed the soaking method of heavy atom replacement which was vital in the successful structure determination carried out at Cambridge. (Hodgkin :1970a).

2. Her early death in 1958 cut short a scientific career of great promise, although her work was carried on by her collaborators, Klug and Holmes, at Cambridge.

I. Fankuchen. In the late 1930's he accepted several more, notably C.H. Carlisle and K. Dornberger. Protein work was stopped by the war, and the X-ray cameras, and a couple of the students moved out of London, in order to reduce the danger of bombing. Carlisle and Dornberger together with the tubes, therefore joined Hodgkin in Oxford for most of the war. (Hodgkin :1970a:6)

After the war the group was re-formed, and developed with a large grant from Nuffield. Much work was done on protein and virus structures, although by this time Bernal was also interested in the structure of water and in practical problems such as the crystalline properties of cement. The group got rather larger in the late 1940's, with the addition of Klug, and assistants to Carlisle, Ehrenberg, and Booth. In the early fifties Franklin joined the group to carry out her own distinctive research. It is clear from remarks made by Hodgkin and Ehrenberg, that by this time Bernal was doing far less research himself -- he had become to some extent an administrator.

3.4 Hodgkin, Cambridge and Oxford¹

Dorothy Hodgkin did an undergraduate degree at Oxford in Chemistry. During her undergraduate years she was interested in a wide range of subjects, and, as has been mentioned, she sat in on the course given by Barker on crystallography. Through Polly Porter, she went to Cambridge in order to carry out postgraduate studies under Bernal at the Cavendish. At first she had no very clear idea of what work she would carry out, but very soon she became interested in biological molecules, and in

1. This section is based on an interview. (Hodgkin :1970a)

particular in the structure of the proteins. She was the joint author, with Bernal of the important 1934 paper on the crystal structure of pepsin. Her work in Cambridge was supported by her Oxford College, Somerville, and in 1934 she returned permanently to Oxford to become College Tutor in Sciences and a University Demonstrator in Chemical Crystallography.

Very little X-ray crystallography was being done at Oxford at that time. Apart from H.M. Powell, and his collaborator, A.F. Wells, who never worked on biological molecules, there was no other activity. Crowfoot started research without any help. In one way she was at an advantage in the rather underdeveloped situation of scientific research at Oxford at the time. She has noted that:

After I came back from Cambridge I was lucky in a way, because I wasn't just Tutor for Chemistry at Somerville College but I was Tutor for all the natural sciences. That didn't mean that I taught all the natural sciences, but it meant that I had to make arrangements for the college teaching of the natural sciences, so that I necessarily made friends in every lab in Oxford. All my friends in Cambridge used to jeer at the idea of having only one science tutor for a whole college, but at that particular moment it was a considerable advantage. (Hodgkin :1970a:13)

In Cambridge she had made many friends from a wide variety of disciplinary backgrounds. She was a personal friend of the Hopkins family, and she attended Needham's lectures. She notes that "in fact my closest friends were in the biochemistry lab". She also knew the Piries very well, and a little later on was a personal friend of Dorothy Wrinch. Thus, she had wide contacts amongst the group of scientists that was most concerned with advances in protein structure in the 1930's. On her return to Oxford she was faced with practical problems of a more immediate kind, however. She notes that:

I wanted to work on X-ray diffraction, of course. There was an old X-ray tube at the top of the University Museum which

had been used for Part II chemistry, but after all the equipment at Cambridge, it was a hopeless thing to come back to. So I went over to Professor Robinson, and I asked him whether there was any chance of getting any money to buy some X-ray equipment. He was very helpful, and we got a grant from ICI for two X-ray tubes and a couple of cameras. The original idea was that this should be put in the organic chemistry department, but this seemed a bit hard on the Department of Crystallography and Mineralogy, so it was installed there. At that time it was housed in the University Museum. After Bowman died it was thought better to split the Department of Crystallography and Mineralogy into two sub-departments. These were (1) The Department of Mineralogy, which became a section of the Geology Department, and (2) the sub-department of Crystallography, which became a section of the Chemistry Department. (Hodgkin :1970a:5)

She started working in quite a small way. In the early stages there were no research students at all, although at this stage there was no difficulty in finding the limited financial support required. Finance got somewhat more difficult when Denis Riley, the first research student came in the late 1930's. During the war the situation changed somewhat:

The next major outside support that we got was as a result of an accident during the war. When war broke out Bernal was called up into the Air Raid Precaution section of the Ministry of Home Security. Everyone thought that London would be laid waste, so he decided to move his apparatus and research students out of London. He made an arrangement to send the main transformer set and apparatus, together with two of his students, to Oxford for the war years. This apparatus he had bought from Phillips in Holland from a Rockefeller grant that he expected to receive, but at the outbreak of war Rockefeller stopped paying grants to Europe, feeling that it would shortly all be over-run. However, since Holland was in enemy hands, Phillips was hardly able to ask for payment for their equipment. So we were in a rather irregular situation, using this equipment, which was our mainstay throughout the war years. So we had C.H. Carlisle, and Katy Dornbergership in Oxford for most of the war, and it was on this equipment that we did most of the work on penicillin.

Towards the end of the war it was decided to take the equipment back to Birkbeck and we thought that we ought to regularise the situation, so Rockefeller finally produced a grant to pay for it. But after that they kept an interest in what I did, and gave us grants. (Hodgkin :1970a:6)

During the war Rockefeller payed very nearly \$10,000 to Hodgkin for work on the X-ray analysis of biologically important molecules. In the years 1945-1955 this sum went up to nearly \$20,000, and in the years 1955-1964 very nearly \$50,000 was made available. (Rockefeller ;1970)

Unlike Perutz, Hodgkin did not work exclusively on the structures of the proteins. During much of the war she worked on the structure of penicillin in collaboration with C.W. Bunn. In the post war years she determined the structure of chloesterol iodide, cephalosporin, and, most important, the structure of Vitamin B₁₂. It was not until 1969 that she and her team determined the structure of insulin, her original protein. By the late fifties and sixties, work on protein structures had become far more of a team effort than it was in the thirties.

Dorothy Hodgkin is an extremely charming and attractive person. This is relevant, because it is possibly one of the reasons why she found it so very easy to make and maintain wide scientific contacts. She made frequent visits to Birkbeck in the postwar period, yet unlike the Birkbeck team, she also maintained satisfactory scientific contacts with the Cambridge workers, and in particular with Perutz. Obviously her high scientific ability was also important in this respect.

Like Bernal and Astbury, Hodgkin is a Fellow of the Royal Society. She was elected in 1947, only two years after the first women were admitted. Unlike Astbury and Bernal, she has received a Nobel Prize -- the Nobel Prize for Chemistry -- in 1964. This was awarded for a "remarkably coherent and well planned series of investigations covering the whole field of organic structures of medical and biological importance". She advanced in status from University Demonstrator

in 1934, to Reader in X-ray crystallography, and finally, in 1960, to Wolfson Research Professor of the Royal Society.

3.5 Perutz, Kendrew, Bragg and Cambridge

3.51 1937-45

The most important centre of British protein X-ray crystallography has been and is in Cambridge. Bernal, Hodgkin, and Fankuchen all worked there between 1932 and 1937. In 1937 Bernal moved to Birkbeck College, London, and W.L. Bragg became the New Cavendish Professor of Physics, so from 1937 to 1946 only Max Perutz was working on biological X-ray crystallography. Perutz, who was a native of Austria, came to work in Cambridge in 1936. His arrival was the result of a rather random series of factors. He had trained, in Vienna University, as an inorganic and organic chemist. He heard of the work of Hopkins and the Cambridge school of biochemistry, and he became very keen to work there. In 1935, the Professor of Physical Chemistry at Vienna, Hermann Mark visited Cambridge, and Perutz asked him to inquire of Hopkins whether the latter would accept him as a research student. Mark forgot to ask Hopkins, but when he got back to Vienna he recalled that Bernal had mentioned that he was looking for a research student. So, despite the fact that Perutz knew no crystallography, he went to the Cavendish.

Bernal did not have any particular problem in mind for his research student, so Perutz spent his first year learning some of the techniques of X-ray diffraction, and studying mineral structures. While on holiday in 1936 he talked to the Professor of Biochemistry at Prague University. The latter was very interested in haemoglobin, and on his return to Cambridge, Perutz asked Bernal if he could work on the structure of this protein. Perutz has written:

(My) scientific work on the structure of haemoglobin started as a result of a conversation with F. Haurowitz in Prague in September, 1937. G.A. Adair made me the first crystals of horse haemoglobin, and Bernal and Fankuchen showed me how to take X-ray pictures and how to interpret them. (Perutz :?:2)

Adair was a worker at the Low Temperature Research Station at Cambridge.

The situation rapidly became difficult for Perutz for two reasons.

Firstly, Austria was occupied by the Nazis, and his parents became refugees, and were thus no longer able to provide financial support.

Secondly, Bernal moved to London, and left him as the only protein worker at the Cavendish. Perutz stayed at Cambridge for two reasons.

Firstly, he was still officially registered as a research student at the University. Secondly, he received a small amount of financial support from his college. Perutz has written about this time in the following words:

Bragg's coming was heralded by the arrival of huge X-ray powder cameras built for the study of metals; they were accompanied by A.J. Bradley, the new head of the Crystallographic Laboratory, and by his assistant, H. Lipson, who had unravelled the structure of complex alloys at Manchester. I felt forlorn among my haemoglobin crystals, doubly so because my native Austria had been over-run by the Nazis, my parents had become refugees, and the money which my father had given me for my studies was nearly exhausted.

I waited from day to day, hoping for Bragg to come round the Crystallographic Laboratory to find out what was going on there. After about six weeks of this I plucked up courage and called on him in Rutherford's Victorian office in Free School Lane. When I showed him my X-ray pictures of haemoglobin his face lit up. He realized at once the challenge of extending X-ray analysis to the giant molecules of the living cell. Within less than three months he obtained a grant from the Rockefeller Foundation and appointed me his research assistant. Bragg's actions saved my scientific career and enabled me to bring my parents to Britain. (Perutz :1970a:183)

Bragg himself has written of the incident, and notes that:

... when Perutz showed me the haemoglobin diffraction patterns I could not but be enthusiastic about their

possibilities. It was at that time difficult to get support in this country for a foreign student, but the Rockefeller Foundation came to the rescue by providing a salary for Perutz as my assistant and an annual grant for apparatus, the total being for £375 a year! (Bragg, W.L. :1965c:3)

The Rockefeller Foundation provided \$3,250 for two years from January, 1939, and further grants which provided for Perutz' salary until 1945, when it was replaced by an ICI Fellowship.¹

Perutz had a distant relationship with Bernal, and a rather closer relationship with Fankuchen. He notes that:

Fankuchen helped me a great deal, and really taught me the techniques of X-ray crystallography Bernal was always away, addressing political meetings. He was an inspiring teacher, always starting things. He had great foresight and enthusiasm. (Perutz :1970b:3)

Later, after the change of personnel at the Cavendish, he notes that:

... I worked in a crystallographic lab. and I was the only protein worker there. One of (the crystallographers) who was important was Arthur Wilson, who was a theoretician, but I did not get much from the metals men. I should have learned more from Wilson, in particular that 99% of the scattering effect would cancel out, but I did not realise this until much later. Really, of all the people in the lab., I learned most from Bragg himself. (Perutz :1970c:2)

At a somewhat later period Bernal and Hodgkin "offered nothing but encouragement" even when no apparent progress was being made, though this was not true of Astbury, who was quite discouraging.

Perutz' contacts were not exclusively in the crystallographic field. Adair has already been mentioned. A very important figure in the development of crystallography at Cambridge was David Keilin, who became Director of the Molteno Institute for Parasitology. Keilin encouraged Perutz, and offered him bench space at the Molteno.

1. Rockefeller :1970; Kendrew :1970a; the account of Perutz' contacts and interests in this section is based largely on two interviews (Perutz :1970b; Perutz :1970c) and a short autobiography (Perutz :?).



When the war started Perutz was anxious to fight against Hitler. He was technically an enemy alien, however, and was hence ineligible. For a number of months he was actually interned, but he was soon released, and drafted into an improbable project by the name of "Project Habbakuk" which was trying to develop enormous aircraft carriers made out of "pycrete" -- sawdust frozen in ice. Perutz was called into this project because of one of his main hobbies -- that of glaciology, as it was felt that his knowledge made him an expert on the structure and habits of ice. During this time he worked in the refrigerated cellars of the Smithfield Meat Market! When the project fell through, he returned to the study of haemoglobin (although even during the period of his absence, some work had been carried out by an assistant).

In 1946, he was joined by John Kendrew. Kendrew had gone up to Cambridge in 1936, and he did Chemistry in Part II. He found organic chemistry boring, but the biochemistry half subject was more interesting and he was influenced by a number of biochemists -- notably Hopkins. He was also strongly influenced by his supervisor, Roughton, who was a physiologist. In 1939, after graduating, he worked for a while under Hughes on physical chemistry. Even at this point he was tending towards biological topics as he was working on enzyme kinetics.¹ Roughton himself, at this time had done no biochemistry, and they attended the same lectures together.

During the war Kendrew was in O.R., and saw a good deal of Bernal and Waddington. Through discussion he became convinced that the

1. Most of this account of Kendrew's career is based on two interviews; Kendrew :1970a; Kendrew :1970b.

structure of the proteins was an important problem and that it should be studied. At the time he thought that he might work with Bernal. However, the latter was short of money, and as Kendrew had an unexpired scholarship at Cambridge he took it up. Kendrew talked to a number of different people at Cambridge for at first crystallography was only one among several possibilities. One of the people that came into contact with him was Perutz who was "isolated at the Cavendish". Eventually he joined him in 1946.

3.52 1947-1962

By 1947 the financial situation was very difficult. Perutz has written:

This was the most difficult time of my life. Bragg's interest in the work continued and he proposed to ask the University to give me a University Lectureship. But this proved extremely difficult because I was a chemist working in a Department of Physics. Being in the Department of Physics I couldn't get a job as a lecturer in Chemistry, and being a chemist, my colleagues in the Department thought I was obviously not qualified to teach physics. I fell between two stools and couldn't get any job at all. By the autumn of 1947 a critical situation had been reached and work was about to close down for lack of financial support for Kendrew and myself. (Perutz :1962a:26)

Keilin suggested to Bragg that he should discuss the possibility of support from the Medical Research Council. Perutz described the meeting as follows:

In traditional fashion, Bragg met Sir Edward Mellanby, the Secretary of the MRC, for luncheon at the Athenaeum Club. Bragg explained that Kendrew and I were on a treasure hunt with only the remotest chances of success but that, if we did succeed, our results would provide an insight into the workings of life on the molecular scale. Even then it might take a very long time before they would bring any direct benefit to medicine. Mellanby took the risk. (Perutz :1970a:185)

He adds elsewhere that this must have been a courageous decision, because Mellanby would have been answerable for any squandering of the slim resources of the MRC. Bragg has described his encounter with Mellanby in similar terms:

After the war I invited the support of the Medical Research Council, frankly saying that the chance of success was indistinguishable from zero, but that the importance of the result was equally indistinguishable from infinity, so the product might be regarded as having a finite value. (Bragg, W.L. :1963a:4)

The result of this was that the MRC Unit for Molecular Biology was set up, with Perutz as its Director. Kendrew was the only other member at first, although it began to grow fairly quickly, with the addition of Crick (who came in 1948), of H.E. Huxley, J.D. Watson, V.M. Ingram, and yet more in later years.

This was the first beginning of the MRC Laboratory of Molecular Biology, which opened in 1962. The role that the MRC has played in the development of protein X-ray crystallography, and more generally in the development of molecular biology in Britain has been very important. Several of the leading members of the MRC Laboratory found it difficult to obtain positions in university departments, because of the interdisciplinary nature of their work and backgrounds. Even with the backing of Bragg Perutz found it impossible to get a Lectureship at the Cavendish in 1947 because his original training was in chemistry. Crick has noted:

... the MRC have supported me all this time And I think this is an important thing -- because I don't see I could have done it very easily in any other way. I was changing my field when I was about thirty -- I had no background knowledge in it. It is very unlikely, I think, by ordinary academic channels that I could have got financial support, and there was a period also when they initially supported us when there wasn't much to show from the work; it was more of an investment on their part, I would say. (Crick :1962a:10)

There was a certain amount of hostility on the part of some biochemists to their new structural neighbours. Kendrew mentions (Kendrew :1970a) as an example that Chargaff viewed molecular biology with disfavour. He also commented on another important point, one touched upon by Crick in the above quotation concerning the fact that the MRC was able to provide a sheltered environment for its workers. This meant that experiments that would produce results only in the long term ++ and the protein X-ray diffraction work was an example of work of this type -- could be carried out with the knowledge that the lack of results did not endanger professional security. (Kendrew :1970b)

Although there was little progress on the protein front, the workers in the MRC laboratory began to produce important results in the very early fifties. This work will be described in greater detail below, and is only mentioned here to show that, to the MRC, the Unit was possibly beginning to justify itself. The first of these was the testing by Perutz, of the proposed structure of the alpha-helix in 1951. The second was the elucidation of the structure of DNA by Crick and Watson in 1953. The third was the development in 1954 of the method of isomorphous replacement in haemoglobin -- an advance which removed the main obstacle to the successful structure determination of proteins. The fourth was the elucidation, by H.E. Huxley, of the mechanism of muscle contraction. Perutz wished to expand the Unit, but he writes as follows:

This was the moment, perhaps, when I should have proposed to the MRC the setting up of a proper Laboratory of Molecular Biology. But was public opinion ready for it, or for that matter, were we? At that time our work stirred up little enthusiasm in this country. When I discussed the implications of Watson and Crick's discovery with a leading geneticist, he assured me that, as far as his subject was concerned, it had none. Most of our crystallographic colleagues continued to be highly sceptical of the prospects of solving protein

structures by X-ray analysis, and it was true that Kendrew and I were still facing great difficulties. I thought it wiser to continue on a modest scale until we felt surer of success. (Perutz :1962b:209)

There were other difficulties. When Bragg retired from the Cavendish in 1954, and moved to the Royal Institution, he wanted to take Perutz and Kendrew with him. They were unwilling to go. Perutz writes:

Bragg's departure was a very unhappy time. Bragg tried very hard to persuade me to go, and Mott at about the same time told me that there would probably be no room available at the Cavendish.

I did not think, however, that the Royal Institution would be a very good place for the MRC Unit to develop; it had very restricted space available and was not attached to a university. Furthermore, the other members did not want to go, and if I moved, the Unit would have broken up.

So I wrote to the General Board of the University pointing out the potential of the field -- I was a university lecturer at the time -- and asked for support. As a result the Board told Mott, who was still at Bristol, that we should not be turned out, and when he came to Cambridge (he) was very helpful. (Perutz :1970c:1)

A compromise was evolved, in which Perutz and Kendrew were appointed readers at the Royal Institution, in order to help build the school up. For this they were paid £100 per annum. (Phillips :1970a:186)

The decision to expand the Cambridge group was not made until the year 1957-1958. By this time the idea was to create a laboratory whose compass would be far greater than that of crystallography alone. Perutz notes that:

By the spring of 1957 the outlook had brightened. Kendrew's work on myoglobin had progressed to a point where we both felt that this structure, at least, would be solved, even though my own work on haemoglobin was still in the doldrums. Sydney Brenner had joined us, and by his dynamic work had created the bacteriophage laboratory in which the recent discovery concerning the nature of the genetic code was made. Ingram had discovered how genetic mutations affect the sequence of amino acids in proteins. Finally, Frederick Sanger, whose famous work on the chemical structure of insulin had also been supported by the MRC, said that he would like to join us. (Perutz :1962b:209)

The response of the MRC was enthusiastic. Sir Harold Himsworth, who was by this time the Secretary of the Council, persuaded the Council to support the project in a single sitting, and the Treasury put forward funds. Perutz continues:

The next problem was the finding of a site. My colleagues and I wanted to carry on within the University where our work would benefit from the interchange of ideas and where we could attract young people. On the University's side our presence was welcomed by many members of the scientific faculties. However, when the proposal was placed before certain officials of the University we were told to put it out of our minds. The University, we were firmly reminded, would not permit any further expansion of research within its precincts, especially if it was divorced from teaching, and it would oppose the setting up of research laboratories by outside bodies in its vicinity.

Fortunately the University's constitution, like that of the United States of America, provides for a system of checks and balances, and no man's word need be taken as final. Nevertheless, in the face of such policy it took a year's negotiation and much hard work by our friends in the University before a suitable site was finally offered to us. Much to their regret, and ours, it proved impossible to find one close to the main science laboratories in the centre of the town, because every available square yard there is already built up or allocated. (Perutz: 1962b:209)

The Laboratory of Molecular Biology is divided into a number of sections, only one of which is primarily concerned with X-ray diffraction. There is a section on protein and nucleic acid chemistry, under Sanger. There is a section on Molecular Genetics under Crick, and there is a section under Kendrew on protein crystallography. In addition, there are facilities for electron microscopy.

3.53 Informal Contacts

In the early fifties there was a certain amount of contact between the Cambridge group and Wilkins at the MRC Biophysics Unit at Kings College London. This has been well documented in The Double Helix

(Watson :1968) which also records that Crick knew and visited Hodgkin at Oxford. There was scepticism about the whole venture on the part of some professional crystallographers. Kendrew notes that: "The professional crystallographers thought we were lunatics", (Kendrew :1970a) and he records that even Fankuchen, who before the war had collaborated very closely with Bernal, felt the work was impossible. It is interesting to note that neither Perutz nor Kendrew were professional crystallographers by original training. In retrospect Kendrew believes that had he been a professional crystallographer, he might well have shared their scepticism. (Kendrew :1970a)

Bragg was very encouraging although he had no clear idea how the structures might be solved. Astbury was important on the "philosophical" side, emphasising the importance of molecular structure, but even he was quite sceptical. (Kendrew :1970a; Perutz :1970b) Discouragement, or lack of interest was evinced from strange quarters. The Delbrück group of phage geneticists was not interested in structural studies at all -- even after the structure of DNA had been elucidated. (Kendrew :1970b)

On the other hand, some of the contacts that Perutz and Kendrew had with other scientists -- not necessarily crystallographers -- were of very important in providing clues and aids to the final successful structure determination.

Thus, the idea for the heavy atom replacement in haemoglobin came from a set of papers by an American physiologist, A. Rigg. When Perutz read the papers he realised that it might be possible to carry out successful heavy atom replacement and hence determine the values of the phases. In the actual replacement work, he was helped by the chemist (and member of his staff) Ingram.

Kendrew was also responsible for a couple of important developments as a result of his non-crystallographic contacts. The first of these was the densiometer. During a visit to Kings College, London, he noticed a densiometer being used by P.B.M. Walker to measure the optical clustering of cells. Kendrew saw how this could be adapted to measure X-ray spots. He used the machine in the evenings, catching the last train back to Cambridge, until the laboratory obtained a commercial version of its own. The second resulted from contacts with the Mathematics Laboratory, at Cambridge which arose because Hugh Huxley was friendly with a maths research student, J. Bennett. EDSAC I, the first computer at Cambridge, was just beginning to work, and Kendrew saw that it would be a tremendous advantage to carry out the calculations on a computer. As a result he learned how to use the machine, despite the scepticism of many others including Bragg and Perutz. At first they were a little unwilling to believe the results, but soon speed (25 minutes on the computer as opposed to four days on the Hollerith Machine) won the day, and other people started asking Kendrew to do their calculations for them. Kendrew notes that he was in danger of becoming the Unit computer operator, and he asked Bragg for an assistant, but Bragg did not see the need.

Kendrew, unlike almost all the other protein X-ray crystallographers with the exception of Bernal, realised that the computing and calculation problems were likely to prove enormous. Phillips notes that:

(In 1950) I saw him at a conference, giving a paper on the use of computers in X-ray crystallography. Now this was long before computers became absolutely essential in crystallography; and most people did things with various other computing aids, of a rudimentary kind. But it was quite clear, at least it's clear to me in retrospect, that at that stage John (Kendrew) saw very clearly that in order to (solve) protein structures rather more advanced computing aids would be needed. (Phillips :1969a:7)

When Perutz described the successful work of Kendrew and Bennett to a conference in North America where there was much talk of the possibility of using computers his announcement caused a considerable stir.

3.54 Students at Cambridge

In the forties and fifties it was quite difficult to recruit good students. In the early days, when the group was still a part of the Cavendish, it was necessary to "sell" the Unit to good Part II students who would go the rounds of the various research sections and decide which section they would like to do research in. The highest prestige area was nuclear physics, and it was followed by low temperature physics in the early days, and then, at a later date by radio-astronomy. The prestige of the MRC Unit was not so high, so they were sometimes faced with students who had put down nuclear physics as first choice, but had not been accepted. They were also the objects of strong and hostile propaganda from certain quarters who wished to dissuade students from entering such an area. At a later date they suffered from lack of proper integration with the teaching structure in the Cambridge Physics Department, and to some extent they have been dependent on American post-doctoral students with their own grants -- U.S. "Cheap labour." (Kendrew :1970b)

One distinctive feature of the postgraduate training offered at the MRC Unit, was the fact that it lasted four years -- with the first year spent doing course-work. They organised no formal lecture courses themselves, but decided for each individual student which were the most appropriate courses.

3.55 Summary

In 1947 Perutz was made head of the new MRC Unit, and Kendrew became its first worker. In 1962, when the Laboratory of Molecular Biology was established Perutz became Director, and Kendrew was made one of the section heads. Perutz was elected a Fellow of the Royal Society in 1954, and Kendrew in 1960. They received a joint Nobel Prize for Chemistry in 1962, for their work in determining the structure of haemoglobin and myoglobin. (In the same year Watson, Crick, and Wilkins received the Nobel Prize for Medicine for their work on the structure of DNA).

3.6 Phillips, the Royal Institution and Oxford

Phillips did a degree in Physics in Cardiff during and immediately after the war. He stayed on to do postgraduate work on the intensities of reflections and the centres of symmetry.¹ In 1951 he obtained his Ph.D. and he went to Ottawa, in Canada, to take up a post doctoral fellowship. He worked for a number of years with W.H. Barnes, who had been assistant of W.H. Bragg's at the Royal Institution, learning how to use computers, and modern equipment in general. (In the immediate post war period the laboratory at Cardiff had been extremely badly equipped.)

Bragg wrote and invited him to come and work on proteins, so in 1955 he returned from Canada and started work at the Royal Institution in 1956. Phillips notes that:

When Bragg had moved from Cambridge, he had attempted to persuade John Kendrew and Max Perutz to come too, but for fairly obvious reasons they wouldn't come. They had, however,

1. Most of this account is taken from Phillips :1970.

promised to help Bragg to build up a school of crystallography at the R.I. Now Perutz didn't do very much, but Kendrew came to the R.I. once a week. He organised the sperm whale myoglobin work at Cambridge, and he got Scouloudi working on seal myoglobin at the R.I., although this was at a later date when the work at Cambridge was already under way. (Phillips :1970:5)

The main workers in the team were U. Arndt, Helen Scouloudi, David Green, A.C.T. North and J.D. Dunitz. They worked very much under the guidance of Kendrew on the structure of myoglobin.

In 1962 they started work on lysozyme, partly through the arrival of an American, Poljak, who had succeeded in making heavy atom replacements of lysozyme. In the year that the structure was determined at high resolution (1965), Phillips and his group moved to Oxford. Although Phillips himself had been initially supported with a grant from the Rockefeller Foundation in his work at the Royal Institution, and did not come onto the MRC's payroll until 1960, most of the others were supported by the MRC from the beginning. It seems that the MRC was fairly keen to see the work moved to Oxford. This can be implied from Phillips' remark that:

... 1966 was the year that Bragg retired. George (Porter, the new Director of the R.I.) was reasonably keen that we should stay there, and I think that had we pressed, the MRC would probably have continued to support the work at the R.I. But the Secretary was quite keen that the work we were doing should penetrate the University work, and I felt that since we had been at the R.I. for ten years that it would be a good idea to take up the challenge of setting up a department and starting a teaching operation. (Phillips :1970:16)

The move was arranged and financed by the MRC on the understanding that the University would take it over as a sub-department, with Phillips as head of department, so in 1966 he was appointed Professor of Molecular Biophysics. In the following year he was elected a Fellow of the Royal Society.

4 THE WORK OF ASTBURY'S SCHOOL IN THE 1920'S AND 1930'S

This section discusses the work that Astbury carried out in the 1920's and 1930's, on protein structure. In the course of this discussion, certain other notions are introduced. Essentially, this chapter argues:

- (1) Astbury started work from a crystallographic background, but during the thirties his interests widened and he became centrally concerned with protein structures in general.
- (2) Parallel to this process, the workers that Astbury referred to came from wider and wider backgrounds.

Necessary detail in the form of a discussion of some of Astbury's papers is given to support the above propositions, and to show that his own view was that crystallographic data was, by itself, insufficient to allow the elucidation of fibrous protein structures.

4.1 Introduction

Astbury was the first professional X-ray crystallographer in Britain to become centrally interested in the structure of proteins. In this section an account of his work from 1926 to 1939 will be given. Although he continued to work both during and after the war, by this time the limelight had moved away from fibrous proteins, and became fixed at first on the final solution to the structure of the α -helix that was proposed by Pauling in 1951, then on the structure of the nucleic acids, and then, last of all, on the structure of the globular proteins.

Astbury graduated from Cambridge in 1921, with a First Class Honours in Physics, although in Part I he studied both Chemistry and

Crystallography (where he had been taught by Hutchinson) (Bernal :1963a:). He went to work under W.H. Bragg, first at University College, London, and then, after 1923, at the Royal Institution, and he became a leading member of the group of young people that included Bernal, Yardley (later Lonsdale), and Cox. He was a breezy, outspoken person, whom Bernal notes as being:

... always brimful of ideas but often these were rather difficult to understand. When he spoke, most people thought he was talking nonsense. I found out fairly early that when Astbury was talking it might appear to be nonsense but it always contained a valuable and new idea. (Bernal :1963a:4)

He started work on tartaric and racemic acid, (Astbury :1923a; 1923b) which were compounds with interesting optical properties, although it turned out that they were too complicated for the methods then available -- it was possible only to determine the unit cells. From this work he went on to collaborate with G.T. Morgan, a chemist, in work on basic beryllium acetate, and tervalent metallic acetylacetonates. This work, like that on tartaric acid, gave early evidence of Astbury's considerable ability to make maximum use of all relevant data -- both crystallographic and chemical. In the later work Astbury made first use of rotation photography that was at this time being developed by Bernal.

In 1924 he collaborated with Kathleen Yardley to publish the space group tables. (Astbury and Yardley :1924) Bragg was very reluctant to see such examples of "mathematical perfectionism" published, and in fact it took the considerable persuasive powers of Astbury to get him to change his mind. (Bernal ;1963a)

In addition to the above work, Astbury was also developing integrating photography -- his own particular approach to the very

difficult problem of intensity measurement in photography.

In this early work Astbury acquired basic crystallographic skills, and made a considerable reputation for himself. His prestige in the Davy Faraday Laboratory was high, and he developed and organised his own research programme. (W.H. Bragg's way of organising the laboratory was laissez-faire in the extreme.)

In 1926 the future must have appeared bright for Astbury. He had made a promising start in organic X-ray crystallography, and there was much more work to do. Yet, at this point, Bragg directed Astbury's attention to a totally new field -- that of X-ray crystallography of fibres. Astbury prepared the photographs of the fibres for Bragg's Royal Institution lecture, but instead of returning to his organic work, he became so interested that he began to spend more and more time on the fascinating and ill defined biological molecules.

4.11 The Move to Leeds

In 1928 Astbury moved to become lecturer in Textile Physics at the industrially oriented Department of Textile Industries at the University of Leeds. This move obviously entailed a considerable commitment to work on fibres -- it was clear that in the foreseeable future Astbury would be unable to undertake extensive investigations of other structures. Both Bernal and Lonsdale suggest that Astbury was unwilling to move to Leeds (Bernal :1963a; Lonsdale :1962b:412), but clearly there was a good deal of persuasion from Bragg, who had been asked to recommend someone suitable for the post. Some of his colleagues at the Royal Institution were clearly unhappy about the field that he was moving into. They thought that there was plenty of relatively simple work on organic crystals waiting to be done, and

that work on such unpromising material as fibres was likely to prove a waste of time. Bernal has written:

I remember well, at the time, how shocked some of us were at Astbury going into this completely complex and very mundane field. We felt that it was very premature -- let us find the structure of regular things first before we tackle the irregular ones. (Bernal:1963a:7)

When Astbury started work on keratin, the field was not only "completely complex and mundane" but it was largely unknown. A small amount of X-ray diffraction work on wool had been carried out by J.B. Speakman and J. Ewles of the Physics Department who had studied wool at various degrees of extension both by X-rays and microscopical means. Speakman proposed that wool was a peptide chain, and although it was not clear what the mechanism for elastic extension might be (elastic extension taking place at up to 34% increase of length over unstretched wool), he assumed that it was the hydrolysis of peptide linkages that caused the plastic extension above 34%. (Speakman :1928) Later, in 1930, he published another paper which examined the degree of crystallinity of wool, and came to certain conclusions about the periods of repeat in the fibrillae in the cell walls.

Although some of this work was actually published after Astbury arrived at Leeds, the bulk of it was done before his arrival. It seems probable that Speakman saw the potential relevance of X-ray studies, but realised that progress might be much faster if they could be carried out by someone who was an expert. It is likely that informal communication between Whiddington (who was Professor of Physics) and Bragg resulted in the latter suggesting that Astbury might like to go and take up the post.

4.2 The Work on Keratin 1930-1935

On his arrival Astbury knew of the German research on the structure of cellulose and silk, and he also became aware of the rather primitive work of Speakman and his colleagues. He immediately launched into a major research project on the structure of keratin which was to result in the publication of three important and "classic" papers in the years to follow,¹-- classic because they helped to determine the direction of much polypeptide research for the next fifteen years.

In the first paper Astbury and Street established a number of important propositions, which can be numbered as follows:

- (1) They showed that all the different animal hairs that they studied gave rise to the same type of X-ray photographs.
- (2) They showed that there were two characteristic fibre photographs -- the α - form seen when the hair was under little or no tension, and the β - form seen when the hair had been extended by about 30%.
- (3) They showed that the α - β - transformation was reversible.
- (4) They established provisional unit-cell sizes for both forms.
- (5) In an addendum they proposed a model for keratin which they claimed explained all the above, as well as other relevant chemical, physical and crystallographic data.

Even at this early stage Astbury was conversant with protein chemistry, he assumed that keratin was a protein, and that it was thus a chain of amino-acids.² His model constituted a polypeptide chain

1. Astbury and Street :1931; Astbury and Woods :1933; Astbury and Sisson :1935.

2. The polypeptide theory of protein structure was fairly well established in the early thirties, but workers were still, to some extent "hedging their bets" on it. (Hodgkin :1970a)

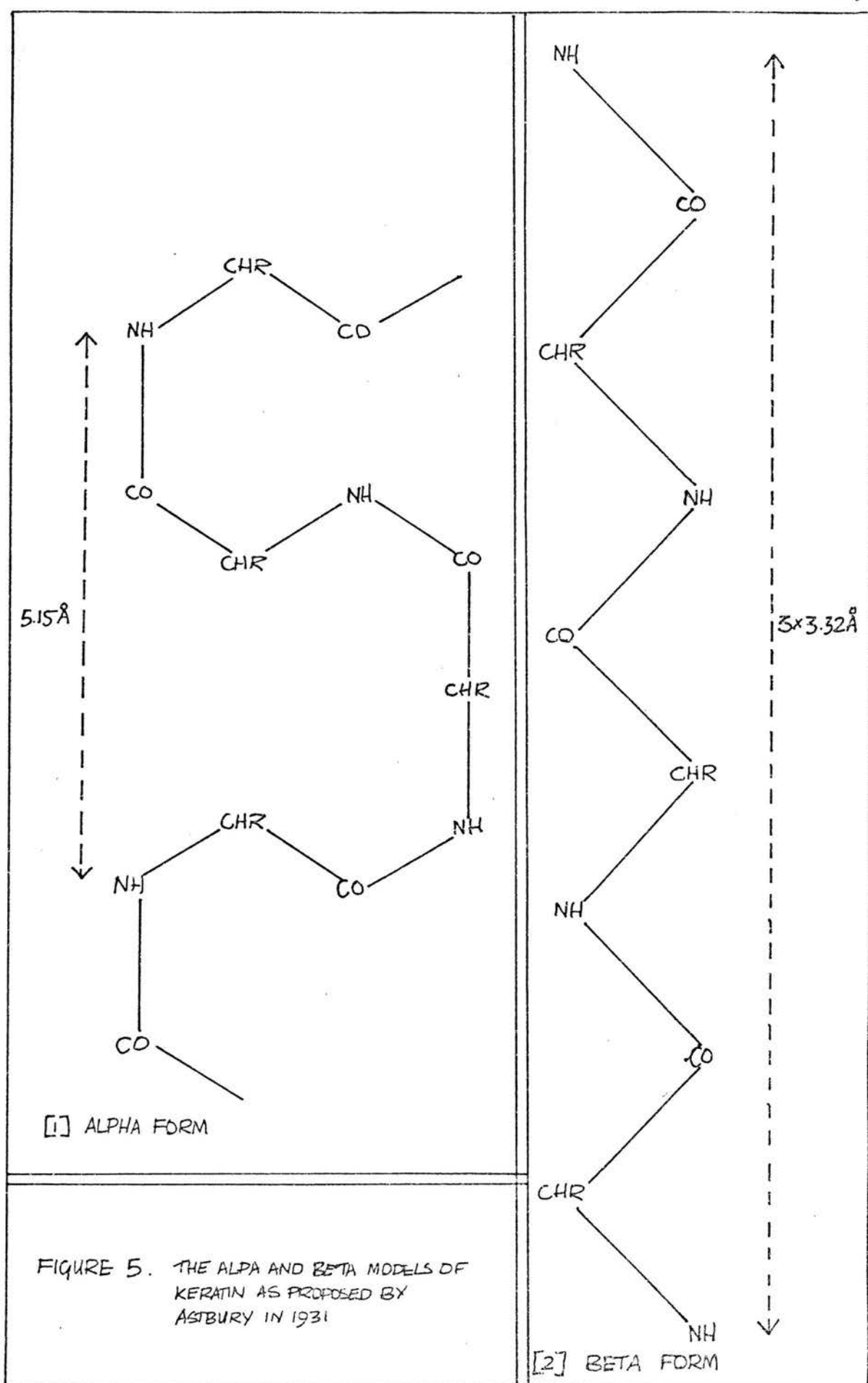
folded in a particular manner. (See Figure 5) He used X-ray evidence to determine the unit cell size of the α - and β - forms. In addition he used direct physical evidence concerning stretching and load extension curves, and he looked at certain contributions from protein chemistry. It is interesting to note that he wrote:

It would not be justifiable at this stage to insist too strongly on the validity of such chemical interpretation as the present X-ray data suggest. Nevertheless, it is true that in a field of the vastness and complexity of protein chemistry, where so much is obscure and yet so full of possibilities, it would be unreasonable to neglect even the faintest hint as to what is the basis of any particular structure type. It is not too much to say that practically nothing illuminating is known of the constitution of the keratins, the proteins from which are built up hair, nails, horn, feathers, etc., and it may well be that the indications of X-ray analysis do actually point the way to a solution, if only we may interpret them correctly. (Astbury and Street :1931:89)

In this paper he looked particularly at cystine, both from a chemical and an X-ray point of view. He took X-ray pictures of cystine, and thereby calculated its unit cell. From a knowledge of the chemical formula, he guessed its three dimensional structure. From further X-ray data, and from a knowledge of the comparative reactivity of stretched and unstretched hair he concluded that it was possible that cystine acted as a bridge between neighbouring keratin chains.

Stepping back from the immediate experimental work, he contrasted the structure of keratin with that of chitin and cellulose. He noted that:

Whatever may be the constitution of the keratins as a class, we are justified by the experimental results now before us in assuming a sound working hypothesis that keratin fibres, like cellulose fibres, owe many of their properties to the repetition along the fibre of comparatively simple units to form molecular chains. (Astbury and Street :1931:96)



By analogy with glucose structure he developed his model for keratin in its unstretched α - form:

We wish to suggest here that the basis of the unstretched fibrous keratins is a series of hexagonal ring systems linked along the fibre axis by "bridge atoms", in a manner analogous to what is generally accepted for the cellulose and related structures. (Astbury and Street :1931:97)

He mentioned that Dorothy Jordan Lloyd in her book The Chemistry of the Proteins had argued that "there must be special structural linkages", and two German chemists, Abderhalden and Komm, had suggested that one form these might take was that of the 2:5 diketopiperazine ring.¹

Turning to a discussion of β - keratin, he noted that the 3.32A spacings that appeared on the photographs were some evidence for the existence of a peptide chain -- the common peptide chain having a periodicity of about 3.5A.

At the end of the paper in the addendum he put forward the model mentioned above -- a model that was not to be altered until 1941. It has similarities with the supposed structures of both cellulose and 2:5 diketopiperazine.

Bernal wrote of this paper:

... it might ... be taken as the key paper of all Astbury's work and well repays reading because it provides the kernel of his discoveries and also gives an explanation as to why he was reluctant to abandon his original ideas. Astbury's work drew on two previous sources, early fibre photographs, the first on wool by Herzog and Jancke as early as 1921 and, secondly, from that of his colleague at Leeds, J.B. Speakman (Bernal :1963a:8)

It can be seen from the above that Astbury was conversant with the work of the protein chemists, vague though it was. Although he did

1. This is formed by the condensation of two amino-acids, but it is not 5.15A. long.

not mention the work of the physical chemists he was probably aware of this too, because within a few months of the publication of the above he had written a paper to Nature on the subject of the molecular weights of proteins. Even at this stage, then, Astbury was being pulled into the fascinating and vague area of protein structure, and what was later to be called "molecular biology". In the paper discussed above he had already used sources far beyond crystallography, and this tendency became more important in his later work.

The second paper in the series is summarised by Bernal in the following way:

Paper II consists essentially of an elaboration and simplification of these observations in the light of more detailed measurements of the elastic properties, carried out in conjunction with Woods. Here there is an attempt to account for some of the anomalies by pointing out that hair is not a homogeneous structure but has marked biological differentiations between cortex and medulla and individual cells, and a recognition that hairs are made with different structures in different parts. Astbury himself considered this the most important of his early papers because it brought together, for the first time in the study of X-rays, the anatomical structure, the physical properties and the molecular structure of a natural material. He used to refer to it as the "wool bible".
(Bernal :1963a:9)

This paper covered work from 1931 to 1933. During this period Astbury and his collaborators made an extensive study of the physical properties of keratin during which they discovered at least three important new facts. Firstly, they established that keratin could be extended by 100% if it was stretched in steam. Secondly, they established that under certain circumstances it could be made to contract to 50% of its original length. Thirdly, they showed that irreversible changes took place if it was stretched in steam to twice its normal length. They called this the phenomenon of "permanent set".

Taking these new facts into account, they concluded that the model that had been proposed in the addendum to the 1931 paper was essentially correct. It was supplemented in the new paper with the notion of "phases". The "phases" were seen to accord to different features observed in the behaviour of hair under extension. Using biological evidence, they suggested that the three phases corresponded to three different parts of the hair. Phase I corresponded to the keratin between the cells, phase II to the keratin in the cell walls, and phase III to the keratin inside the cells. His data on the structure of hair came both from one of his former colleagues at Leeds, A.B. Wildman, and from d'Arcy Thompson's book Growth and Form. It would, he argued, be natural to expect the cell walls to be more crystalline than the inter or intra cell material, and this corresponded to the greater definition in the X-ray photograph of Phase II. This also fitted with other work that he was doing in collaboration with Bernal and Marwick on the structure of the cell wall of Valonia Ventricosa. Phase III, which was the most protected, was also the most resistant to chemical and physical change.

Finally, he returned once more to the structure of keratin. The β -form appeared to be a fully extended polypeptide chain, with side chains projecting out alternately from one side and the other. From further study of the diffraction data he determined the average dimensions of the amino-acids in wool. From the very approximate chemical evidence available, he was then able to calculate a figure for the density of hair which corresponded to that found experimentally. This was confirmed by work carried out by Hughes, Rideal, Gorter and Grendel, on the density of protein monolayers.

In this paper he noted that the diffraction data from a substance as messy as hair was not at all good. In a footnote he wrote:

Owing to an inherent lack of definition and paucity of reflections, the translations and spacings of X-ray photographs of biological subjects can rarely be measured with any great accuracy. (Astbury and Woods :1933:371)

In this series of papers he was evidently trying to obtain the maximum information possible from the X-ray photographs. He did this by improving techniques (developing devices to scale hair and take better tension photographs) and by taking photographs in a wider variety of situations. In addition, he made use of data from all possible relevant sources. Thus, it can be seen from the above that he not only drew data from crystallography, but also from physical chemistry, protein chemistry, surface chemistry and biology. If his citations are any guide, then he was becoming more conversant with a wide range of literature on proteins.

In the third paper in the series (Astbury and Sisson :1935) he attempted three tasks. Firstly, to quote Bernal, "he attempts to impose a second orientation on the keratinous fibres". In his summary of the paper, Astbury wrote:

When keratin fibres are squeezed laterally in the presence of steam or hot water, they are transformed first into β -keratin, and then the β -keratin crystallites rotate about their long axes so as to bring the protein side-chains normal to the plane of flattening.

It is thus shown by direct measurement that the "backbone spacing" and the "side chain spacing" are at right angles, just as had already been proposed from indirect evidence. (Astbury and Sisson :1935:550)

Secondly, he brought much more extensive biological data into the discussion of secondary orientation. Thirdly, he engaged much more directly in discussion about protein structure in general, bringing in evidence from the studies of globular proteins, and physical chemistry.

His developing interest in general protein theory is reflected by the fact that he clearly felt that there existed much more general rules, applicable to both fibrous and globular proteins.

The paper started with a frank admission of the difficulties of X-ray crystallography as a technique for studying fibres. The passage quoted below can be seen as a summary of the difficulties of fibre X-ray work, and an attempt to come to terms with implied questioning by non-biological X-ray crystallographers:

One of the difficulties associated with the X-ray study of biological structures arises from the fact that such structures, while not in general unorganized "powders", are nevertheless usually built up of numerous submicroscopic individuals of continuously varying orientation: in the typical biological "fibre" for example, the imperfectly crystalline molecular aggregates all lie with one and the same crystallographic direction either approximately parallel to the fibre-axis or spirally inclined at some approximately constant angle to it; but subject to this limitation there may be present within the compass of the X-ray beam all orientations up to the maximum possible consistent with axial symmetry. This means that although we may not be condemned to work in the least profitable field of X-ray technique, that of the completely random "powder photograph", yet we are debarred from the full geometrical advantages to be derived from operating with a single macroscopic crystal. Speaking briefly, the main trouble lies in the difficulty or impossibility of measuring sufficient inter-directional angles to define the molecular arrangement without ambiguity. Sometimes it is possible to draw very plausible conclusions, or even conclusions that are almost certainly correct; but in others the diffraction effects are so ill-defined as to preclude altogether the use of direct geometrical argument, and compel us to fall back on indirect reasoning based on evidence from various sources, including comparative photographs of related structures. The X-ray investigation of proteins in particular is a many-sided enquiry of this nature, for the diffraction effects are susceptible of interpretation only in relation to other physical and chemical data. The X-ray photographs then serve to give form, so to speak, to such data -- to provide the three dimensional framework necessary to build them into a coherent whole. (Astbury and Sisson :1935:533)

This puts the problems facing the fibre crystallographer of the 1930's in a nutshell. Given the inadequacy of the data, it was necessary to seek further data from non crystallographic sources. (However, it is

doubtful whether W.L Bragg and A.J. Bradley of the Manchester Physics Department would have accepted that powder photography was less profitable than X-ray work on hair. Astbury's paper was written at the time of the greatest triumphs of the Manchester school, and the structures that were being determined by Bradley were much less complicated than protein molecules.)

The main substantive conclusion of this paper has already been mentioned above -- the fact that the chain "backbone" and the "side-chains" were at right angles to one another. He also came to the conclusion that the keratin grids (i.e. the keratin chains connected by side-chains) were narrow, and that in the tabular hair crystallites they lay on top of one another. He went on to discuss the microscopic structure of wool, using both this knowledge of the crystallite structures and new biological evidence adduced by J.E. Nichols of the Wool Industries Research Association, of Leeds. (The latter had concluded that wool was not made of spindle shaped cells, but rather of tabular cells. Astbury's concern was with the orientation of the crystallites in the cells.

At this point he introduced the recent work of Bernal and Crowfoot on the X-ray diffraction of pepsin (Bernal and Crowfoot :1934) and wrote:

Bernal and Crowfoot have obtained a series of X-ray oscillation photographs of unchanged crystalline pepsin from which they have drawn the conclusion that the pepsin molecule is probably spheroidal in shape, just as had been calculated already from the results of experiments with Svedberg's ultracentrifuge. On the other hand, it would appear to follow from a mass of other X-ray and related data, chiefly on protein fibres that all proteins, in the molecular sense, are either actually or potentially fibrous; either polypeptide chains always pre-exist in the molecule, or they may be formed on comparatively light changes in the environment. (Astbury and Sisson :1935:548)

Further discussion of the relationship between globular and fibrous proteins will be deferred until the last section of this chapter, for the simple reason that by this stage Astbury had become so deeply involved in general discussions about protein structure that it is virtually impossible to discuss his contribution in isolation from other work being carried out.

4.3 Keratin and Myosin

It was natural that biological X-ray crystallographers should be interested in the structure of muscle. In 1934 Astbury wrote:

To physiologists, perhaps, all X-ray studies of protein fibre structure are only by way of apprenticeship to a much more serious task, that of elucidating the molecular mechanism of muscular activity. Muscle, to be sure, has been photographed frequently enough by X-rays -- the pioneer efforts are again due to Herzog and his colleagues -- but the immediate problem is now to discover the structure of the muscle protein myosin which has been shown by Boehm and Weber to be mainly responsible for the diffraction pattern given by muscle itself.... (Astbury :1934a:22)

In many respects the diffraction patterns of myosin appeared very similar to those of keratin. By stretching muscle it was possible to obtain a β - photograph, although this could only be done under somewhat exotic conditions. He postulated a similarity between the phenomenon of muscular contraction and that of supercontraction of hair, but did not find that this was easy to demonstrate. In 1935 with his physiological colleague, Dickinson, he appealed for help from the protein chemists, asking why keratin which appeared to be constructed on a similar pattern to myosin, was less extensible than the latter. Was it, he wondered, because of large amounts of cysteine in the keratin? Were they, as he put it, "to conclude that the hair protein is roughly speaking no other than "vulcanised" muscle protein?" This appeal was repeated in 1936. (Astbury and Dickinson :1936:909)

A further paper, covering much the same ground, exploring the analogy between myosin and keratin, and noting the fact that no third type of X-ray photograph could be seen under conditions of supercontraction, appeared in 1940. Here, too, he discussed the relationship between globular and fibrous proteins, and offered another warning about the limitation of X-ray techniques:

The X-ray diffraction patterns must be considered only in the light of all sorts of supplementary evidence, rather as broad sketches hinting at the detailed picture. This principle was followed always in the X-ray studies of keratin already presented, and a similar line of approach is attempted here. (Astbury and Dickinson :1940:325)

In this paper he discussed the amino-acid composition of the proteins (taking his evidence from Barritt and King, Speakman and Bailey), and again pointed to the differences in the cysteine content. He noted that X-rays had shown that there were only two basic types of protein fibres -- the extensible (such as keratin and myosin) and the inextensible (such as collagen). He suggested that it would be very useful to know more about the amino-acid composition of the two types. The notion that there were relatively few types of protein was supported by Svedberg's analysis, and by the work of Bergmann and Niemann.

4.4 The 1941 Model of Keratin

In 1941 Astbury published a paper in which he acknowledged that the critics of his long standing model of α - and β - keratin had put forward arguments that were fatal to this model. He proposed a second model.

The important criticisms of the old model had concerned acceptable molecular configurations. The original α - structure, with its hexagonal rings (see Figure 5) on the main polypeptide chain, had in

this respect a similarity to the controversial "cyclol" hypothesis that had been advanced by Dorothy Wrinch in 1936.¹ Within a couple of years of the formulation of the cyclol hypothesis a majority of protein chemists and X-ray crystallographers felt that the cyclol structure, if not impossible, was at least highly unlikely. This issue generated a good deal of heat. The rather fortuitous similarity between the cyclol "cages" and the hexagonal α -keratin rings precipitated the difficulties for Astbury's model. In the course of detailed discussions of the feasibility of the cyclol theory a number of structural chemists had attacked Astbury's model (even though the work of chemists such as Pauling and Niemann depended to some extent on Astbury's data). Thus, they wrote:

... the X-ray studies of silk fibroin ... and of β -keratin and certain other proteins by Astbury and his collaborators have provided strong, (but not rigorous) evidence that these fibrous proteins contain polypeptide chains in the extended configuration. (Pauling and Niemann :1939:1860)

They went on:

The X-ray work of Astbury also provides evidence that α -keratin and certain other fibrous proteins contain polypeptide chains with a folded rather than an extended configuration. The X-ray data have not led to the determination of the atomic arrangement, however, and there exists no reliable evidence concerning the detailed nature of the folding. (Pauling and Niemann :1939:1861)

In his paper (Astbury and Bell :1941) Astbury noted the similarities between his first structure of α -keratin and the Wrinch cyclol hypothesis, and wrote that:

... the tide of evidence is flowing strongly against ... (this type of folding), and especially the experiments of Neurath with up-to-date scale models have shown conclusively that there is simply no room for the side-chains when the main-chains are folded in this way. It seems that we have to accept the fact once and for all and bend ourselves to seek a new solution. (Astbury and Bell :1941:697)

1. The cyclol controversy is discussed in detail in a later chapter.

No objection had been raised to the original β - structure. The conditions which the model had to fulfil were as follows:

- (1) The α - form must be about half as long as the β - form.
- (2) The density must remain practically constant.
- (3) The folds must repeat at a distance of about 5.1A.
- (4) The side-chains must stand out alternately on one side and the other of the plane of the fold.
- (5) The folds must be nowhere so sharp as to leave insufficient room for the side-chains.

(Astbury and Bell :1941:697)

Since the globular proteins had a density of 1.3 both before and after denaturation, he argued that this was "one of the best arguments that we have in favour of regarding these proteins as effectively fibrous". He inferred a general structure of folding in polypeptides, in which the side chains project alternately above and below the plane of fold of the backbone. Working on this basis, he argued that if the other conditions were to be satisfied then 5.1A. was the shortest distance in which a polypeptide chain could be folded so as to leave the side chains sticking out alternately on one side and the other side of the fold. He postulated a square fold, with sides of 5.1A. length. The result of this was that the amino-acid side chains were:

... seen to be grouped in close-packed triangular columns first on one side of the fold and then on the other.
(Astbury and Bell :1941:698)

Certain distortions were introduced into the chain in order to allow for a hydrogen bond between the CO- and NH- groups within the fold. Then he went on to write:

The above solution of the keratin-myosin problem has been obtained by induction, but the more correct treatment would appear to be by deduction from the principle of close packing. The principle is familiar enough in structures built from

ions and small molecules, but it must apply also to the mobile parts of single large molecules, such as the side-chains in proteins. (Astbury and Bell :1941:699)

The objections to his first model had clearly led him to become much more conscious of structural chemical limitations, while his use of the hydrogen bond foreshadowed the role that it played in the generally accepted model of the α - helix proposed by Pauling in 1951. Later, Bernal wrote that::

(the idea of the intra-chain hydrogen bridges) particularly appealed to Astbury because it showed that the whole structure of proteins depended on the side chains acting not as main linking chains -- as he originally considered -- but essentially as packing elements which put together the hydrophobic side chains and separated them from the hydrophilic elements. The doubling of the α form on stretching becomes no longer an accident but an inevitable consequence of the close packing of side chains in a simple regular pattern. (Bernal :1963a:12)

4.5 Other Work

4.51 Collagen

Astbury did most of his work on the extensible keratin-myosin group, but he also wrote two papers on the inextensible collagen and gelatin group. In the first of these (Astbury and Atkin :1933) he discussed the dimensions and molecular weights of the amino-acids in gelatin. From X-ray and density data he deduced that there was a repeat unit of 2.8A. along the main chain. When water attacked gelatin its effect, like that on keratin, was mainly on the side chain spacing.

In 1934, at the Cold Spring Harbor Symposium (Astbury :1934a) he suggested that the repeat of 2.8A. (which represented the length of an amino-acid residue) was maintained by internal chemical linkages:

that is to say, linkages not necessarily between the side-chains of neighbouring main-chains, but most probably between

those of one and the same main-chain. (Astbury :1934a:21)

Taking the argument somewhat further, he noted:

The X-ray photographs of collagen and gelatin suggest also that the amino-acid residues are somehow grouped in sets of three. The fact that the main-chains are characterised by a succession of permanent internal folds or constrictions necessarily involves some arrangement of the sort, and it is encouraging to find ... additional evidence in favour of the number three. (Astbury :1934a:22)

The 'additional evidence' referred to the amino-acid composition of gelatin.

He did not return to collagen and gelatin until 1940. (Astbury and Bell :1940) He noted that no structure of collagen-type proteins had been postulated, and he suggested that this had been due to lack of data. With new data which was becoming available, this should now be possible.

He reviewed Bergmann's recent and very much more reliable data on the amino-acid composition of gelatin. This appeared to fit with the Bergmann-Niemann scheme.¹ Two thirds of the amino-acids (except for one residue in eighteen) were accounted for with glycine, hydroxyproline, and proline, and the number of residues in the gelatin molecule was probably a multiple of 72. Considering the frequency of some of the less frequent amino-acids, and the X-ray data collected by Wyckoff, Corey, Clark and others about meridional spacings representing great distances, it seemed to Astbury that:

Their data are best explained by a sequence of 4 times 72 residues in a row, grouped in approximate sets of 12, 24 and 36. This gives a molecular weight of about 27,000, or a multiple thereof, corresponding to Svedberg's gliadin class. (Astbury and Bell :1940:422)

1. This theory, put forward by the two important American protein chemists, stated that the total number of amino-acid residues in any protein, and also the total number of each kind of amino-acid, was expressible in terms of the formula $(2^n \cdot 3^m)$, where n and m were intergers. Also constituting part of the theory was the proposition that the amino-acids were distributed at constant intervals along the polypeptide chain.

This paper was a shortened version of the First Procter Memorial Lecture, of which Bernal has written:

This was his first exercise into following the actual sequence residues (sic) in a fibrous protein, and it is very interesting how close he came to the subsequent explanation. (Bernal :1963a:14)

4.52 Nucleic Acids

Bernal has written:

Perhaps Astbury's greatest contribution to molecular biology were the first steps he took in unravelling the structure of nucleic acids. This was no accident. Astbury was convinced of its importance (Bernal :1963a:18)

In 1938, when Astbury first published on DNA (then called thymonucleic acid) both the structure and the function of the nucleic acids was unknown. Pollock has recently written that the:

biological role (of the nucleic acids), in so far as it was formulated at all, tended to be considered in the nature of structural support for the gene protein -- or (at the best) as what was referred to by Darlington as a 'midwife' molecule to assist non-specifically, in enabling the protein of the gene to replicate itself.

The constant association of nucleic acids with "self propagating" systems such as chromosomes and virus was, however, being stressed by workers such as Caspersson and Astbury, but with reproduction by a direct copying process analagous to crystallization. (Pollock :1970:13)

In January 1938, Signer, Caspersson and Hammarsten published a letter in Nature (Signer, Caspersson and Hammarsten :1938) in which they described how, by means of a study of viscosity and double refraction of flow in solution, they had deduced that sodium thymonucleate was in the form of long thin rods, at least 300 times longer than they were wide, that the molecular weight was between half a million and a million, that the rods polarized light perpendicular to their long axis, and finally that they must contain strongly doubly

refracting components arranged in a definite pattern. From the latter they concluded that the purine and pyrimidine rings must lie in planes perpendicular to the longitudinal axis of the molecules. The molecular weight corresponded to that determined by Svedberg in the ultracentrifuge.

Astbury reported that he had obtained "a striking, though still somewhat obscure, X-ray fibre photograph" which appeared to have a repeat unit of 3.3A. -- the same as β -keratin. The repeat unit he supposed to correspond to the nucleotides. He wrote:

The significance of these findings for chromosome structure and behaviour will be obvious. It seems difficult to believe that it is no more than a coincidence that thymonucleic acid consists of a long succession of nucleotides spaced at a distance so nearly equal to that of the long succession of amino-acid residues in a fully extended polypeptide. Rather it is a stimulating thought that probably the interplay of proteins and nucleic acids in the chromosomes is largely based on this fact, and that some critical stage in mitosis, involving the elongation of the protein chains, is realized in close co-operation with the dominating period of the interacting nucleotides. (Astbury and Bell :1938:747)

In the same year, at the Cold Spring Harbor Symposium, he wrote:

The idea is equivalent to saying that the molecule of thymonucleic acid fits so perfectly on the side-chain pattern of a fully-extended polypeptide chain that interaction should take place almost without any steric hindrance whatsoever; most easily between the basic side-chains and the phosphoric acid groups, but presumably too, between the acid side-chains and the basic groups of the nucleotides. Furthermore, the products of the combination should also be fibrous, like the two original constituents. (Astbury and Bell :1938a:113)

He went on to describe an experiment in which clupein (a protein) was combined with thymonucleic acid. The resultant X-ray photograph was only marginally different -- one of the principal side axes changed, and this is what would have been expected if the protein chain had attached itself to one side of the thymonucleate column. Finally Astbury speculated still more freely:

The chief components of the chromosomes are apparently compounds of protamines and nucleic acids. We have thus a first experimental indication of the direction of the protein chains in the chromosomes, namely, along their length, and therefore a reasonable molecular basis for the linear sequence of genes demonstrated by the cytologists. Knowing what we know now from X-ray and related studies of the fibrous proteins, how they are built from long polypeptide chains with linear patterns drawn to a grand scale, how these chains can contract and take up different configurations by intramolecular folding, how the chain-groups are penetrated by, and their side chains react with smaller co-operating molecules and finally how they can combine so readily with nucleic acid molecules and still maintain the fibrous configuration, it is but natural to assume, as a first working hypothesis at least, that they form the long scroll on which is written the pattern of life. No other molecules satisfy so many requirements. (Astbury and Bell :1938a:114)

Although he did not publish any further papers on nucleic acids, he maintained his interest in the area after the war, and recent unpublished evidence suggests that he was working on nucleic acids in the late forties. (Olby:1970) In 1950 he wrote:

The proteins lie at the corner of the business, we may be sure of that, and the attack on them must go on unceasingly; but they are not, or have not come to be, entirely self-acting, and it is little less urgent -- it is a parallel problem -- to concentrate also on their collaborative macromolecules, notably the polysaccharides and nucleic acids, especially the nucleic acids. Many investigations in recent years have brought out and emphasized the importance of the nucleic acids in biosynthesis: as far as we can see, they are absolutely essential components in chromosomal processes and cell multiplication and in virus reproduction, and in fact it is largely believed now that the nature of the interaction of the proteins and nucleic acids is probably the supreme issue of all in the chemistry and physics of life. (Astbury :1951:38)

4.53 Other Work

During the 1930's Astbury also carried out a certain amount of work on the structure of cell walls of simple vegetable systems. This will not be discussed here except to note that it involved collaboration with R.D. Preston of the University of Leeds Botany Department. The first of these papers (published in 1932) was written

jointly with Bernal, who describes this work as "slightly minor" although "very interesting and successful". (Bernal :1963a:17) This work is a good example of Astbury's considerable interest in biology and ultrastructure.

Astbury also did much applied work -- work that was technically and industrially oriented. In addition he wrote papers on methods of X-ray analysis.

4.6 General Protein Work

It has been suggested above that the scope of Astbury's interests and contacts became wider as the 1930's progressed. This process will now be further illustrated in a discussion of his more general work on protein structures.

It has been noted that Astbury started his career in protein X-ray diffraction with a detailed study of keratin, and he discovered what had not previously been established -- namely that keratin could take up two configurations, the α - form and the β -form. His major work on keratin culminated in the construction of the 1931 model, and its reformulation in 1941. The data upon which the 1931 model was based fell initially into three main classes:

- (1) X-ray data, which while vitally important, never, as both Astbury and Pauling pointed out, led the way to an unambiguous structure.
- (2) Purely physical data about the extension of wool.
- (3) Chemical and protein chemical data of various sorts, concerning in particular, the amino-acid composition of wool. In addition there was the fundamental chemical assumption that proteins were polypeptide chains.

Although these were the most important influences on the early keratin work, there were several other sources of data that came to be useful in the work on proteins. The most influential, initially, was the work of Svedberg and his collaborators, on the molecular weights and shapes of proteins. Not only did this work confirm that proteins were macromolecules, but it also suggested that they could be seen as falling into certain classes from the point of view of their molecular weights. It seemed within the limits of accuracy available at the time, that all proteins had molecular weights which were a multiple of the basic number 34,500.

4.61 Protein Work: 1931

Although the Svedberg work was important, it posed problems for the worker interested in fibres. Fibres are of indefinite length, even at a molecular level, and the problem as to what constituted the molecular weight of a fibre was hence considerable. This objection was absent in the case of the globular proteins, and Astbury was very interested in the fact that Svedberg had discovered proteins of 34,500 times 1, 2, 3 and 6 molecular weight. It suggested to him that there was some crystalline effect which brought together fundamental units of this weight, with radii 22.5A. (from Gorter and Grendel's work). In 1931 he wrote:

The suggestion arises ... that, provided we can explain the occurrence of the weight 34,500, the rest may be merely another aspect of that grouping of molecules which is called crystalline. But if this is so, we have to account for the non-occurrence of the number 4, (Astbury and Woods :1931:663)

He postulated that the polypeptide chains might be held together by cross linkages in pairs, triads, or sixes, as well as occurring singly. His explanation of the fundamental unit of 34,500 was simply

that disruptive resonance would occur with increasing probability with increasing length of chain, and that 34,500 represented the maximum probable length.

4.62 Protein Work: 1934-1935

With the work of Bernal and Crowfoot in 1934 Astbury turned his attention to the relationship between the fibrous and the globular proteins. He wrote:

It was difficult, of course, to reconcile (findings about the fibrous nature of globular proteins) with external morphology and the Law of Rational Indices, but the photographs of Bernal and Miss Crowfoot, taken before the degeneration which we now see the crystals must have undergone on drying, clear up this long-standing problem at once. Furthermore, their photographs tend to confirm the suggestion that the numbers 2, 3, 4 and 6 occurring in Svedberg's multiple particle weights are fundamentally of crystallographic significance, even though their conclusions to date appear to be against the chain mechanism proposed for the building-up of the various crystallographic groups. (Astbury and Lomax :1934:795)

None the less, he still believed that there was a close relationship between globular and fibrous proteins, and this was partly because of work that he had carried out on dried pepsin. In a paper published in 1935 (Astbury and Lomax :1935), he pointed out that most denatured proteins gave poor quality powder photographs, which were similar to photographs of β -keratin, despite the fact that their molecular weights varied greatly. What was the relationship between globular and fibrous protein? He wrote:

The answer to the question must be in three parts as follows: (i) all the proteins photographed are peptides or combinations of peptides; (ii) increasingly marked crystallinity ... is an expression of increasingly marked degeneration or denaturation; and (iii) the completely denatured state is that in which the peptide chains have been freed from any specific configuration and aggregated into regular bundles, or crystallites, held together by two principal linkages, the backbone and side-chain linkages (Astbury and Lomax :1935:850)

He speculated in similar terms elsewhere:

We are thus confronted with the question of whether the chains in the "degenerate" state are formed by the metamorphosis and linking-up of originally globular molecules, or whether the true original unit is the chain itself, which is afterwards folded into some specific design after the manner of the mammalian keratin transformation. (Astbury and Sisson :1935:548)

He next floated an ingenious idea -- that feather keratin, upon which he had done a certain amount of work, was an actual example of the way in which fibrous proteins evolved from globular proteins through a process of linear condensation. He argued as follows: Firstly, there are strong similarities between the periodicities observed in feather keratin and those observed in pepsin. Secondly, Svedberg has shown that there is probably a uniform size of protein unit, and in any particular protein a typical number of these units comes together. Thirdly, fibrous proteins are periodic polypeptide chain systems -- in other words, fundamental units of one kind make them up. Was it possible, he asked, that feather keratin was an example of this process in action? Was it a condensed series of smaller units? After mentioning similar arguments put forward by Bernal and Crowfoot, he wrote:

From this point of view the fundamental protein units are always comparatively compact, and elongated molecules are produced by further regular condensation in a specific direction; and it would mean this, that just as the globular proteins on "degeneration" give rise to irregular aggregates of polypeptide chains, so, under proper directive control in the living organism, can they be built up into the regular, periodic chain-systems characteristic of the stable fibrous proteins. (Astbury and Sisson :1935:549)

He mentioned the production of collagen by fibroblasts as an example of the sort of process that he had in mind. But his final purpose was to try to combine the results of his studies on keratin, with more general ideas about the manner of protein production. He felt that:

... it seems more likely on general grounds ... that the keratin molecule grows, not by a process of deposition on a prepared protein framework, but by a process of end-to-end polymerization or condensation. (Astbury and Sisson :1935:549)

4.63 Protein Work: 1937-1939

At this point, Astbury, together with Gorter and van Ormondt of the Hospital for Children's Diseases at Leyden in the Netherlands, utilised a purely formal approach to the question of protein structure. (Astbury, Bell, Gorter and Ormondt :1938) They attempted to build up a protein-like structure by laying down layers of polypeptide chains that had been liberated from globular proteins. They concluded from this work that globular proteins were not curved monolayers because the density of such a system was lower than that actually observed in globular proteins. How else might globular proteins be built? One possibility was four disks of monolayer, of about 22.5A. radius, placed on top of one another, and separated by their side-chains. This work grew from a great variety of sources -- it was, in his own words, a "generalisation" of the work on keratin, using the notion of a folded polypeptide chain with its side chains sticking out from either side. It also fitted with data derived from Svedberg, Bernal, and of course Gorter and Grendel, each of whom had calculated the radii of globular proteins.

In a paper in 1937, Astbury made use of the recently formulated Bergmann-Niemann Hypothesis, and new evidence from Bernal and his collaborators about the structure of tobacco mosaic virus. Here he argued once again that the original distinction between fibrous and globular proteins was beginning to disappear. He wrote:

One possible way, based on density and other considerations, of deriving a general scheme directly from keratin amounts actually to building up molecules having essentially the structure deduced from X-ray data for keratin crystallites, and this suggests at once the idea that the protein fibre crystallites and the tobacco virus units fall into the same category. (Astbury ;1937a:968)

He noted that various proteins appeared to conform to the Bergmann-Niemann scheme in terms of minimum molecular weights. X-ray diffraction permitted the calculation of average molecular weights for the residues, and knowing this, it was possible to work, via the Bergmann-Niemann hypothesis, to the total molecular weights of the proteins, and hence, if the scheme was correct, to the Svedberg molecular weight classes. With the help of Woods he carried out the necessary calculation for keratin, and concluded that although the scheme appeared to work "it is yet difficult to prove that only powers of 2 and 3 are involved".

In the same paper he described a possible drawback to the Bergmann-Niemann hypothesis -- namely that it would lead to clashes between different amino-acids for the same "position" along the chains¹. Although the whole situation was still very unclear, and the hypothesis was open to objections, he concluded on an optimistic note:

... it seems clear that we are now on the fringe of something very fundamental indeed in protein theory, and the moral value alone of Bergmann and Niemann's discoveries will be immense. Exact analysis of the proteins, though always laborious, need no longer be the thankless tasks they have been. There is a goal in sight. (Astbury :1937a:969)

During the next couple of years much heat was raised by the cyclol controversy, and Astbury and Bell contributed their share in a letter published in Nature in 1939. (Astbury and Bell :1939) The debate about the cyclol theory took place on two rather different fronts. Firstly, there was a debate about whether the cyclols were probable

1. E.g., if two amino-acids repeated every eighth and ninth place, they would clash for position 72.

molecules, in connection with chemical evidence and theory. Secondly, there was a debate about whether Patterson vector diagrams were being correctly by Wrinch in order to support the cyclol hypothesis. The latter debate was a purely technical crystallographic debate, and is discussed in detail in a later section. Astbury entered the fray not on the crystallographic front, but on the chemical side. This is perhaps an indication of where, by the late thirties, his main interests lay. His attendance at the Klampenborg meeting is further evidence of his basically biological interests.¹

At the beginning of the war the debate on protein structure to some extent died down. This was partly due to the fact that many of the main protagonists were caught up in war work, and partly because of the disruption of communication caused by hostilities.

1. The Klampenborg meeting was a small informal conference attended by scientists from a number of different disciplinary backgrounds. Waddington has recently written of the meeting:

The participants were W.T. Astbury, P. Auger, H. Bauer, J.D. Bernal, C.D. Darlington, B. Ephrussi, A. Fischer, L. Rapkine, H. Stubbe, N.W. Timofeeff-Ressovsky, C.H. Waddington and K. Zimmer. Physics was represented not only by quantum theory men such as Auger and Zimmer, but by X-ray crystallographers such as Astbury and Bernal: this was the first time that there was a real meeting of geneticists and crystallographers. (Waddington :1969:318)

The main subject of discussion was the nature of the genetic material at a molecular level, and it was from this meeting that Astbury evidently derived some of his ideas about the function of nucleic acids.

5 WORK ON GLOBULAR PROTEINS IN THE 1930'S: BERNAL AND HIS COLLABORATORS

5.1 Introduction and Summary

If there is a single figure who dominates the prehistory of molecular biology then it is J.D. Bernal. His scientific work was important both in its own right and in what it started. The structure of the sterols, the study of the crystalline proteins, the study of viruses -- in all these areas Bernal contributed and started lines of research. He also made important contributions to work on the structure of metals and water, and to the methods of oscillation and rotation photography. When this work is added to his non-scientific achievements then the magnitude of his intellectual power and energy and the breadth of his interests becomes clear.

This chapter covers the development of Bernal's work on proteins and viruses, and includes a discussion of the work of some of his students. It is also in part an introduction to the more systematic treatment of the protein work that follows in Chapters Six to Nine.

5.2 Bernal's Early Work

Bernal was one of W. H. Bragg's pupils at the Royal Institution. His first paper was on the structure of graphite which he successfully determined in 1924 although his second paper, on rotation methods of X-ray crystallography published in 1926 was probably more important

(Bernal :1926)¹. In this paper Bernal provided charts for the X-ray worker to read off the crucial variables from the photographs, without need for any calculation. This paper brought Bernal wide recognition among English speaking crystallographers, even though the idea of the reciprocal lattice had been known in Germany for a number of years.

In 1927, Bernal moved to Cambridge, and for the next ten years he carried out much of his fundamental work on the structure of metals, biological molecules and water.

His first biological work was on the sterols. In 1932 he published a paper in Nature (Bernal :1932a) reporting X-ray studies on a number of sterols, including ergosterol. The unit cells and space groups of ergosterol and some of its irradiation products were measured and compared, and they were found to be similar to one another. This paper represented a considerable triumph for Bernal in two respects. Firstly, it identified ergosterol as a single substance, rather than a complex of several. Secondly, and more important, it showed that the conventional chemical structural formula was incorrect. This was done rather simply. Once the dimensions of the molecule were established by crystallographic means, it was evident that the conventional structural formula would not fit into the required space. Robertson has

1. The rotation method is a relatively direct way of determining and indexing crystal reflections, and assigning them to appropriate reflecting planes in the crystal. It does this by constructing a "reciprocal lattice", in which every plane in the real crystal lattice is represented by a point. Planes that are close together in real space are represented by points that are far from the origin in reciprocal space, and vice versa. A "sphere of reflection" is constructed to the same scale as the reciprocal lattices and reflections occur when points on the reciprocal lattice cross or touch the surface of the sphere, when the one is turned at an origin relative to the other. From this very simple idea, it becomes very easy to determine the indices of most reflecting planes.

described this work as an "exceptional case of great importance" (Robertson :1962a:152), and indeed it was exceptional by comparison with the general lack of success of organic X-ray crystallography in the middle 1930's. Much later, Bernal wrote:

.... in close connection with the Biochemical Laboratory of Professor Hopkins, work was started, first on amino acids and then on the sterols. There, owing to what was effectively a happy chance of being able to discover, by X-rays in the first place, the correct carbon skeleton of the sterols, Bernal was able to unify the structure of these important bodies which were then of particular interest in connection with vitamins and sex hormones. (Bernal :1962a:380)

The work on sterols was collected and fully published in 1940 in the Philosophical Transactions of the Royal Society in a joint paper written by Bernal, Crowfoot-Hodgkin, and Fankuchen. (Bernal, Crowfoot and Fankuchen :1940). This paper developed a general classificatory scheme based on the nature and size of the unit cell.

Bernal also worked on Vitamin B₁, water and further simple organic compounds in the early 1930's. This work will not be discussed here.

5.3 The Work on Pepsin

The work on globular proteins started rather suddenly as a result of a serendipitous discovery. Hodgkin and Riley have written:

The history of the X-ray analysis of protein crystals began for many of us when the first X-ray diffraction photographs of single pepsin crystals were taken in 1934. The crystals were hexagonal bipyramids, 2mm long or more, prepared by John Philpot while he was working for a short time at Uppsala. He had left his preparations in the refrigerator while he was off on a skiing holiday and on his return he was astonished to find how large his crystals had grown. He showed them to Glen Millikan, a visiting physiologist from California and Cambridge, who said, "I know a man in Cambridge who would give his eyes for those crystals". Philpot naturally offered him some crystals to take back in his coat pocket and so Millikan took them to J.D. Bernal.

It was very lucky for protein crystallography that Millikan took the crystals in the tube in which they were

growing in their mother liquor. This enabled Bernal to make his first critical observation: that the crystal (sic) lost birefringence when removed from their liquid of crystallization. He observed only a vague blackening of the film when the X-rays were passed through the dry crystal. Therefore he mounted some crystals in their mother liquor in Lindemann glass tubes. The wet crystals gave individual X-ray reflections, which were rather blurred owing to the large size of the crystals and the large size of the crystal unit cell, but which extended all over the films to spacings of about 2.A. That night, Bernal, full of excitement, wandered about the streets of Cambridge, thinking about the future and how much it might be possible to know about the structure of proteins if the photographs he had just taken could be interpreted in every detail.

During the next few days when (Dorothy Crowfoot Hodgkin) returned to the laboratory from a brief absence, many more X-ray photographs were taken and calculations were made on the possible weight of the asymmetric unit in the pepsin crystal. There were also consultations with friends among the biochemists to find out what was already known about proteins and protein crystals. The picture obtained was complicated; it was clear the crystals, as crystals, had unusual properties. Professor Hopkins described how he had isolated large quantities of lecithin from partly purified crystals of egg albumin; the lecithin molecules presumably fitted in between the protein molecules in water-containing spaces. Bernal found an old paper by Schimper (1881) in which he recorded the swelling and shrinking of protein crystals under different conditions of humidity and their penetration by large dye molecules. Svedberg had recently begun to measure the molecular weights of protein molecules in the ultracentrifuge. The order of magnitude he found for pepsin, about 40,000, was large; it fitted with the size of unit cell indicated by the X-ray data, given that the c-dimension of the unit cell was probably twice the minimum value recorded. (Hodgkin and Riley :1968:15)

In the pepsin paper the molecular weight of the unit cell was provisionally calculated as 478,000, which was twelve times the Svedberg molecular weight. Although it was not possible to determine molecular structure or detailed molecular arrangement, the authors went on to argue:

From the intensity of the spots near the centre, we can infer that the protein molecules are relatively dense globular bodies, perhaps joined together by valency bridges, but in any event separated by relatively large spaces which contain water. From the intensity of the more distant spots, it can be inferred that the arrangement of atoms inside the

protein molecule is also of a perfectly definite kind, although without the periodicities characterising the fibrous proteins. (Bernal and Crowfoot :1934:795)

One important result of the demonstration that pepsin possessed a definite structure was that biochemists were no longer able to argue that proteins were agglomerates without a determinate form. So, as in one sense, Astbury had indirectly proven the polypeptide chain theory of protein structure, so Bernal, in another way, demonstrated the specific chemical identity of globular proteins.

The relationship between the fibrous and globular proteins was far from clear in 1934. In the final sentence in the quotation above, Bernal and Crowfoot implied that pepsin might not be constituted of polypeptide chains. They argued:

The observations are compatible with oblate spheroidal molecules of diameters about 25A, and 35A. arranged in hexagonal nets, which are related to each other by a hexagonal screw-axis. With this model we may imagine degeneration to take place by the linking up of amino acid residues in such molecules to form chains as in the ring-chain polymerisation of polyoxy methylenes. Peptide chains in the ordinary sense may exist only in the more highly condensed or fibrous proteins, while the molecules of the primary soluble proteins may have their own constituent parts grouped more symmetrically around a prosthetic nucleus.

At this stage, such ideas are merely speculative, but now that a crystalline protein has been made to give X-ray photographs, it is clear that we have the means of checking them and, by examining the structure of all crystalline proteins, arriving at far more detailed conclusions about protein structure than previous physical or chemical methods have been able to give. (Bernal and Crowfoot :1934:795)

It looked as if the molecules underwent a radical change on drying as the adjacent letter by Astbury (Astbury and Lomax :1934) reminded readers that powder photographs of pepsin exhibited evidence of chain structure. Hodgkin recently commented as follows:

We thought that (the polypeptide chain theory of protein structure) was extremely probable, and the question was, how did it get organised? In the letter to Nature which I

wrote with Bernal, Bernal was, of course, the senior person, and there were some ideas in there which I would have changed had I been able to. Bernal didn't know very much about protein chemistry and some of his ideas were wildly speculative. But I would say that on the whole we implicitly believed the theory, although there was a certain amount of guarding of remarks, in case it turned out not to be true. (Hodgkin :1970a:13)

Non-polypeptide theories were quickly abandoned, partly as a result of work by Philpot who showed that neither exposure to X-rays nor drying had any appreciable effect on the enzyme activity.

In summary, the paper on pepsin was important on two counts. Firstly, it opened up the whole field of crystalline proteins to investigation by means of X-rays. The molecules and particularly the unit cells were seen to be very large, but on the other hand the difficulties they presented were purely as a result of their size. Secondly, and this was important both from the point of view of the X-ray crystallographers and the biological community, after this work there was no possibility that the proteins were anything other than perfectly determinate large molecules.

Once this first success was achieved, a great extension of the protein work became possible. During the next five years, from 1935 to 1939, Bernal and his pupils studied a large number of proteins, and in addition, worked on the structure of viruses. Without extremely detailed historical work it is difficult to separate the work of Bernal, Hodgkin, Fankuchen, Perutz, Carlisle, and Riley, and to determine the origin of a given idea. A summary of the papers written by the above authors is given in the following sections.

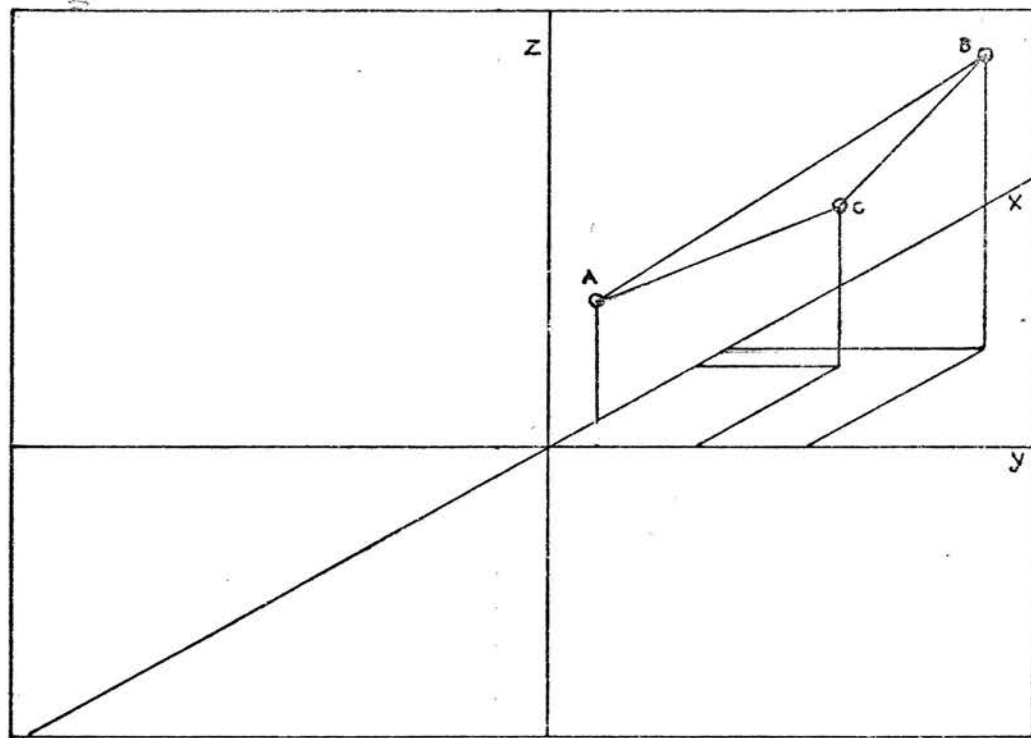
Two events of importance to the protein workers occurred in 1935. Firstly, W.M. Stanley succeeded in crystallising tobacco mosaic virus thereby opening its study to X-ray crystallography. The second event of importance was the invention, by the Canadian crystallographer

A.L. Patterson, of the "vector method" which was a further attempt to get round the phase problem. It was universally known as the Patterson method. Without knowing the phases of the diffracted X-rays it was impossible to determine the locations of the diffracting atoms. However, Patterson showed that it was possible to calculate a vector structure which revealed a certain amount about the structure without a knowledge of the phases.¹ This was important because it meant that Patterson (vector) diagrams might permit the determination of protein structures -- or at least the identification of certain gross structural features.

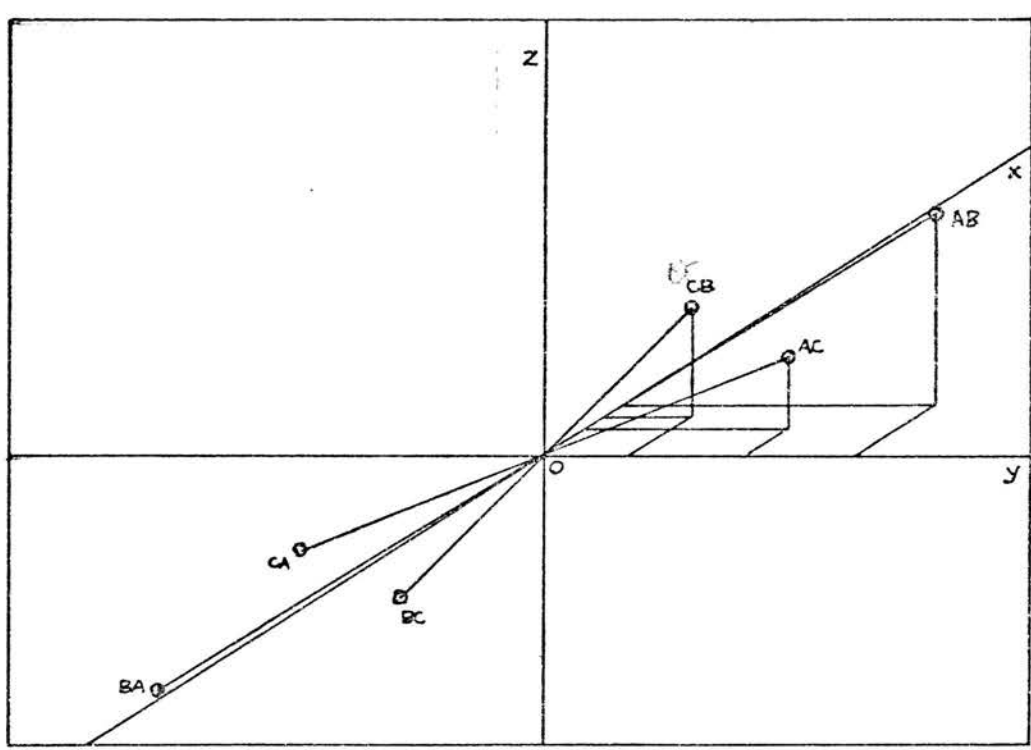
5.4 Hodgkin's Work

After her return to Oxford, Hodgkin soon started work on insulin. She became friendly with the Professor of Chemistry, Professor Robinson, who received a great many crystals through his wide contacts. The first insulin crystals were a gift from Boots the Chemists, to Robinson. He passed them on to Hodgkin, knowing that she was interested

1. A Fourier series converts data about the intensity and phase of diffracted beams into data about the electron density of the matter producing the diffraction effect. In the absence of knowledge of the phases, intensity data can be used to calculate a vector structure. This vector structure, when displayed in a "Patterson diagram" represents the distances and angular relationships between all pairs of atoms in the structure, every vector being shifted so that one of its ends lies at a common origin. In Figure 6 an atomic structure and its equivalent vector structure are illustrated. However, since for n atoms in the unit cell there are $n(n-1)$ maxima in the unit cell of the vector structure, the difficulty of unambiguous interpretation of vector structure for complex molecules is obviously large.



[a] ATOMIC STRUCTURE WITH THREE ATOMS IN UNIT CELL



[b] EQUIVALENT VECTOR STRUCTURE

FIGURE 6 ATOMIC AND VECTOR STRUCTURES

in proteins¹. She was "extremely enthusiastic" as she had been looking for a possible protein to work on. By taking X-ray diffraction pictures she rapidly determined the size of the unit cell, and she then went on to make a guess at the molecular weight.

She has also noted:

At about this time, we also discussed the problem of the structure of insulin with C.R. Harington at University College Hospital, who pointed out that insulin was doubtfully to be classified as a protein and suggested lactoglobulin as a more typical protein for study by X-rays and one very recently crystallized. R.A. Kekwick, from the same laboratory produced crystals in two modifications, orthorhombic and tetragonal, that were the next crystals to be X-ray photographed. Actually the most beautiful lactoglobulin crystals, orthorhombic plates 2-3mm across, arrived unlabeled through the mail one day and were recognized immediately. They came from Lindström-Lang by way of Bernal to Oxford and they marked our first contact with Lang and Copenhagen. Yet another preparation was made in Oxford by Ogston As a consequence, lactoglobulin was the first protein from which single crystal diffraction data were obtained when the crystals were both wet and air-dried. The relations between the two suggested strongly that the protein molecule was essentially unchanged on drying. (Hodgkin and Riley :1968:18)

The first paper on insulin was published in the middle of 1935 (Hodgkin :1935a). The size of the unit cell and the size of the molecule were all determined, and by comparison with pepsin, insulin was seen to have a relatively compact structure.

A second paper, reporting the results of Patterson calculations, was published jointly with Riley in 1939. (Hodgkin and Riley :1939) These were the first Patterson projections for a protein, and the calculations were carried out entirely by hand -- a very laborious business. It was immediately clear, however, that:

there would not necessarily be any simple means for interpreting the Patterson functions for insulin such as those

1. Most of this account is taken from two sources: (1) Hodgkin and Riley :1968; (2) Hodgkin :1970a.

used by Patterson himself for copper sulfate or hexachlorbenzene. The insulin maps did however indicate that there were, within the insulin crystals, objects concentrated at interatomic distances of 10A and 22A, distances observed by Astbury in the fibrous proteins. There were other features too of the insulin vector patterns that invited attempts at further interpretation. (Hodgkin and Riley :1968:19)

Hodgkin corresponded with Patterson about possible ways of further interpreting the projections, but Patterson confessed that "for the moment I do not see how this can be done". In a later letter Patterson regretted that due to circumstances outside his control he was unable to start "Madly calculating and possible experimenting on proteins". Ewald also offered a suggestion for a possible explanation of the projection¹. Wrinch, too, was busy with the data, arguing that it supported the cyclol theory. The main firm result of this work, however, was that it confirmed that the insulin molecule was a rigid unit.

Work on lactoglobulin was carried on simultaneously with that of insulin, although the former was much disrupted by the outbreak of war. Hodgkin notes that:

That year, vector maps were calculated from very limited data for both wet and air-dried orthorhombic and tetragonal crystals, and many efforts were made to interpret these. These were abandoned after the war as it became clearer how much more data it was both necessary and possible to collect to solve the structures in detail. (Hodgkin and Riley :1968:20)

This work went ahead slowly, partly because Hodgkin was doing other work on the side. She has recently noted that:

... our interest in the proteins certainly didn't mean that we weren't interested in doing other things. We could see that we weren't going to be able to do these things immediately. We could see that the order of magnitude of difficulty of these crystals was much higher, and this was a result of the size of the molecular weights and the unit cells. Of course, we had rather little experience of them at the time. But

1. This information comes from Hodgkin and Riley :1968.

nonetheless, we were always looking for possible ways of going further, and we had this idea of going further right from the beginning. So the problems that we saw were actually those of getting heavy atoms which would be heavy enough to effect the phase angles significantly. My own idea about how to make progress was to do simpler things first, but I have never at any time completely stopped work on insulin. I held it by my while trying out methods of structural analysis on simpler molecules -- the sterols, penicillin, but I suppose that I always saw the structure of insulin as a goal. In the earlier period I tended to work on it myself, and encouraged other people to work on other things.
(Hlodgkin :1970a:4)

5.5 Bernal, Fankuchen and Perutz

Bernal and his collaborators continued to work on proteins. In 1938 he, Fankuchen and Perutz published a paper in Nature summarising their work on two proteins, chymotrypsin and haemoglobin. They gave unit cell dimensions and estimated the molecular weight of both proteins, comparing their own estimates with those calculated by ultracentrifugal techniques. Once again, the reflections were much clearer for the wet than for the air-dried crystals. There were, however, few details for spacings of less than about 8.0Å. They wrote:

The explanation is probably somewhat as follows. The intensity of a reflection from a protein crystal may be considered a function of three factors: the structure factor due to the position of the molecules, that due to the positions of the atoms inside the molecule, and a third factor depending on the regularity of arrangement. It is apparent that there is general enhancement of spots in the regions of 9Å. and 4.5Å. corresponding to the two main reflections maxima of denatured proteins. In the dry protein, however, the irregularity is such that only the first of these is retained, the spots corresponding to the outer rim being generally too weak to register. If this analysis is correct, it follows that the change involved on denaturation does not require any considerable movement of atoms or amino-acid residues, but only relatively minor rearrangement together with almost complete loss of regularity, the dry protein representing an intermediate stage. (Bernal, Fankuchen and Perutz :1938:524)

They went on to argue:

As can be seen from Fig. 2 the dried crystals of chymotrypsin show not only alterations of spacing but also of relative intensities of reflection. If we assume that drying takes place by the removal of water from between protein molecules, studies of these changes provide an opportunity of separating the effects of inter- and intra- molecular scattering. This may make possible the direct Fourier analysis of the molecular structure once complete sets of reflections are available in different states of hydration. (Bernal; Fankuchen and Perutz: 1938:524)

This was the first published hint of one of the two ways of surmounting the phase problem that Bernal proposed in the following year -- that of the swelling and shrinking method.

In the same issue of Nature Hodgkin and Fankuchen wrote a short paper on tobacco seed globulin, in a preliminary attempt to determine the molecule weight.

At the end of 1938 an interdisciplinary conference on the structure of the proteins was held by the Royal Society in London. It was opened by Svedberg (:1939). Hodgkin was reported, no doubt in brief, as saying:

The number of protein crystals studied by X-ray methods is still small, chiefly owing to the difficulties of applying this technique to crystals of such low X-ray reflecting power. Most of the crystals also readily lose water on exposure to air, forming new collapsed crystal structures in which the arrangement of the units, as indicated by further decrease in the intensity of the X-ray reflexions, is considerably disorganized. So far, of only seven proteins -- pepsin, insulin, excelsin, lactoglobulin, haemoglobin, chymotrypsin and tobacco seed globulin -- have sufficient X-ray measurements been made to cover even the first stages of crystallographic examination, the determination of the unit cell size and cell molecular weight. An of these only three, lactoglobulin, haemoglobin and chymotrypsin, have been studied both wet and dry. (Hodgkin :1939a:74)

At the same meeting Bernal (:1939a) argued that the best way to determine protein structures was to deduce them from X-ray data.

However, he noted:

So far unique solutions are not to be expected and cannot indeed be found, but the choice of structures can be still further narrowed by invoking our knowledge of the chemical and physico-chemical properties of proteins and of the lengths of bonds and of atomic radii established by X-ray analysis of simpler structures. (Bernal :1939a:75)

Although the Svedberg and the crystallographic molecular weights often coincided, the crystallographic data provided only a certain amount of support for the Svedberg classes -- support which was certainly not conclusive. Bernal also discussed the 4.5A. and 9.0A reflections found in both fibrous and crystalline proteins. Astbury had shown that in the case of the fibrous proteins they represented the distance between neighbouring peptide chains corresponding to side-chains and "backbone". Bernal assumed that a similar explanation should hold for the crystalline proteins. On the basis of Hodgkin's Patterson projection of insulin, he speculated about insulin structure, noting in a side reference to the cyclol hypothesis that:

To find (the) ... positions (of the scattering matter) we must depend not on a priori structures with arbitrary assumptions, but on an exhaustive study of the number of point combinations that can give the observed peaks. (Bernal :1939a:76)

Covering a number of possibilities, he noted that the most plausible insulin structures were composed of twenty-four sub-molecules. He argued thus:

" We now have considerable confirmative evidence of a physico-chemical nature for this assumption, as protein molecules have been split into submolecules by various agents. As to their structures, we can legitimately speculate without the addition of any new assumptions that they consist of regularly folded peptide rings containing possibly twelve amino-acid residues held in shape by hydrogen links between adjacent CO and NH groups. Models of these can be made which have external dimensions of about 10A and prominent internal distances of about 4A. A protein molecule built up in this way would not only account for the X-ray evidence but would give a plausible explanation of denaturation phenomena. Reversible denaturation would consist of the separation and possibly the unfolding of the submolecules; irreversible

denaturation in their conversion into long-chain molecules by the familiar mechanism of ring-chain polymerization. (Bernal :1939a:77)

He concluded by arguing that much more research would be needed before a firm model could be developed, and he appealed for greater co-operation between X-ray crystallographers and others, suggesting that:

It would be of enormous value to have some form of central bureau for protein research which would facilitate exchange of information and material in this field, and assist an ordered attack on the whole problem. (Bernal :1939a:77)

5.6 Perutz and the Early Work on Haemoglobin

To judge by the volume of publication, Bernal and Fankuchen were more preoccupied with virus structures than that of protein at this time. Perutz, on the other hand, was developing his work on haemoglobin. This was first reported in Nature in 1938 (Bernal, Fankuchen and Perutz :1938). In 1939 he published a paper giving data collected by non X-ray crystallographic means (Perutz :1939a). He examined the strong pleochroism exhibited by haemoglobin, using both sheep and horse methaemoglobin, and horse oxyhaemoglobin, in an attempt to determine the orientation of the haem groups in the molecule. The 1938 paper had suggested that the four haem groups were related in pairs about a two-fold axis, By means of the new data, Perutz proposed that they might lie at the corners of a square (a suggestion already advanced by Pauling).

In 1942 Perutz published the results of his attempt to develop the "swelling and shrinking method" that had been proposed in a joint paper with Fankuchen in 1938. In the new paper (Perutz :1942a) Perutz outlined the method very briefly, and then noted :

Single crystals of horse methaemoglobin can be made to contract so slowly that the complete drying process occupies several days. In addition, it was found possible to arrest the contraction over periods of weeks at stages of hydration intermediate between the wet and the air-dried, leaving sufficient time at each stage to record the reflexions from the principle crystal zones. (Perutz :1942a:491)

He noted the change in unit cell size during this process, and discovered that background diffuse reflections increased relative to Bragg reflections with increased drying. He calculated Patterson projections for four points in the wetness-dryness process, and superimposing them showed that there was a marked similarity in both the locations and shapes of the peaks. From this he came to a number of conclusions. Firstly the crystal was rigid along the b axis, and this suggested that the molecules were linked together in this direction. It followed from this, and symmetry considerations, that the molecule must be about 64Å. long in this axis. Secondly on the basis of optical and X-ray data, it was known that the haeme groups maintained their orientation in relationship to the a and b axes. From this he concluded that:

This orientation can be maintained only if the molecules form coherent sheets extending through the crystal parallel to the c plane, with layers of water and probably ammonium sulphate between the protein sheets. On drying, the layers move together and simultaneously slip over one another, thereby increasing the monoclinic angle. (Perutz :1942a:493)

The third conclusion concerned the thickness of the protein sheets. Here the inadequacy of the swelling and shrinking method was rather apparent.

The thickness of the protein sheets could be considered:

if it could be decided which of the peaks ... are definitely of intramolecular origin. It can be shown that if two corresponding peaks at different shrinkage stages coincide and are closely similar in shape, then it is highly probable that they belong to the intramolecular type. On the other hand, if two peaks do not coincide, it does not necessarily follow that they are not of the same type. (Perutz :1942a:493)

From the vector diagrams the water layers were seen to be at least 15A. apart (that is to say, the protein sheets were ~~at least~~ 15A. thick). Yet, because of the size of the unit cell, they could not be greater than 35.6A. From these, and from symmetry considerations, there were only two possible arrangements. Either there were two sheets of protein, 18A. thick, with water in between, or there was no water, and the protein was a single rigid sheet. "No decision between these two possibilities can be made at the moment." Fourthly, Perutz refuted some suggestions put forward by Neurath and Polson the protein chemists, about the axial ratios of dried haemoglobin molecules.

A further paper, on the structure of oxyhaemoglobin was published by Perutz in 1942 (Perutz :1942b). He noted that although:

the present preliminary survey of the crystal structure has not led to any new information regarding the molecular architecture of oxyhaemoglobin, it has already given some useful hints about the way in which the molecules are arranged in the crystal. (Perutz :1942b:324)

The crystals were very unstable -- he had to take all the pictures in a cold room, and even so the X-rays so damaged the crystal that it was impossible to take a second acceptable picture from the same crystal.

He compared the Patterson projections of oxyhaemoglobin with those of methaemoglobin, and noted a number of similarities between the c projection of the former and the a projection of the latter. From this he went on:

If we assume that there is no difference between the general molecular architecture of the oxyhaemoglobin and methaemoglobin -- an assumption which is reasonable both on chemical and crystallographic grounds -- then the correspondence between the two maps indicates a similarity between the orientation of the haemoglobin molecule with respect to the c plane in oxyhaemoglobin on the one hand and the a plane in methaemoglobin on the other. (Perutz :1942b:324).

Finally he discussed the orientation of the haem groups in oxy-haemoglobin, on the basis partly of optical, and partly of vector data.

5.7 Prewar Work on Viruses

Bernal and Fankuchen wrote a number of papers on virus structure in the late 1930's. Bawden, a virologist, wrote in 1942:

Of the many techniques introduced into research on viruses during recent years, none has aroused more interest than those of the crystallographer. The value of these techniques in such work is amply shown by three recent papers by Prof. J.D. Bernal and Dr. I. Fankuchen. The authors describe these papers as "only a preliminary and rough survey" and state that "many more years of work will be needed before exact and reliable interpretations can be expected". No doubt this is true. Nevertheless, what has already been done has greatly widened our understanding of viruses, in addition to bringing to light unsuspected properties of colloidal aggregates. (Bawden :1942a:321)

Bawden was in a very good position to know, having been involved in some of the first work himself.

In a paper published jointly by Bawden, Pirie, Bernal and Fankuchen (:1936) various crystallographic, chemical and infective tests on tobacco mosaic virus (TMV) were reported. The experiments were carried out on three types of TMV, and these each produced their characteristic disease when they were innoculated into plants, even though no gross chemical or physical differences were apparent. Each kind of TMV had "the usual analytical figures" in terms of protein composition, although there were traces of phosphorous and carbohydrate which were attributable to the presence of nucleic acid. The effects of the orientation of the solution in a magnetic field were also described. On being left to stand, the solution dried on the surface and produced three layers. The first was an extremely

soft gel which was well oriented, and had high birefringence. The outer part of the gel shrank by 50% forming a layer of higher refractive index but lower birefringence. The third layer was dry and slightly translucent. The authors went on to write:

The X-ray patterns of these different forms show remarkable similarities and differences. For the large angle scattering there appears to be little difference, except in general intensity, between patterns given by all the different forms from the top liquid, oriented by flow in a Lindemann glass capillary, to the dry gel and the "crystals", from ammonium sulphate solutions. This pattern is therefore entirely due to the protein molecules themselves and may be called the intramolecular pattern. It appears to have about the same order of complexity as that produced by feather keratin, with a repeat unit in the fibre direction of $3 \text{ times } 22.2 \pm 0.2 \text{ \AA}$. (Bawden, Pirie, Bernal and Fankuchen :1936:1052)

In order to measure the distant X-ray spacings a special camera was constructed. The sideways spacings between the rod-like molecules were measured and the different layers proved to give different spacings. In the case of the dry gel, there were five lines, which corresponded to the first five possible reflections in hexagonal close packing. The distances in this case were about 152Å. The wet gel gave three lines which also corresponded to hexagonal close packing at a distance of 210Å. The liquid gave three lines, one of which (at a spacing of 100Å.) was of intramolecular orientation, and the other two of which varied from 300Å. to 470Å., depending on the concentration of the solution. The authors suggested that these results were most explicable in terms of a parallel series of rods. No indication of regularity in the other directions was obtained. Finally, they wrote:

From the results already gained, it is legitimate to make certain conclusions as to the nature of the protein molecules. First, the molecules seemed to be identical in cross-section. Secondly, each molecule has quasi-regular structure and thus may be considered to be built up of

sub-units of approximately the same character. The physical properties of the substance can best be explained by postulating rod-shaped molecules. The minimum cross section area of these is 20,100 sq. A. for the dry gel. The molecular length is more uncertain. The extreme character of the orientation phenomena and the X-ray data point to a minimum length of not less than ten times the width, or greater than 1,000A. This gives a minimum molecular weight in reasonable agreement with Svedberg's estimate of 17 times 10^6 , though there is nothing to show that the lengths of the molecules are uniform.

These results have a certain intrinsic interest, but this would naturally be greatly enhanced could it be shown that these rods are in fact virus particles. This conclusion seems to us both reasonable and probable, but we feel that it is still not proved, nor is there any evidence that the particles we have observed exist as such in infected sap. (Bawden, Pirie, Bernal and Fankuchen :1936:1052)

The camera which Fankuchen devised for this work was very ingenious.

Bernal wrote of Fankuchen's contribution:

He excelled in the devising of apparatus specially tailored for the purpose. One problem was that of examining the liquid crystals at very low angles, and for this monochromatic X-rays were essential. He devised an X-ray monochromator made of a pentaerythritol crystal sliced in such a way that it could give a very narrow beam of strictly monochromatic radiation of high intensity. (Bernal :1964a:917)

Two years later Bernal, Fankuchen and Riley (:1938) reported further experiments, this time on tomato bushy stunt virus. The crystals were too small for single crystal analysis, so powder photography was used. Spacings of 100 and 279A were observed. They concluded from this that the lattice was body centred with a side of 394A., and the virus particle had diameter of 340A. The molecular weight was estimated to be in the region of 12,800,000 -- very different from the centrifuge estimate of 8,800,600. The discrepancy was possibly due to differences in water content.

The work on viruses was fully reported in a wide survey published in 1941 (Bernal and Fankuchen :1941a; 1941b; 1941c). After a discussion of the preparation of virus solutions, the authors looked at inter-molecular structure, noting that the electron microscope suggested

that the virus particles were about 1,500A. long. They went on to discuss internal structures of the viruses and the biological implications of the work. In their conclusion they wrote:

Even in solution, they have an inner regularity like that of a crystal. Virus preparations are thus in a sense doubly crystalline. Closer analysis reveals that the X-ray patterns are not directly comparable to those of a crystal as many of the reflections do not obey Bragg's law, but can be understood on the theory of gratings of limited size. The structure seems to consist of sub-units of the dimensions of approximately 11A cube, fitted together in a hexagonal or pseudo-hexagonal lattice of dimensions -- $a = 87A$, $c = 68A$. Contrary to what earlier observations seemed to indicate, the particle seems to be virtually unchanged by drying and must therefore contain little water. There are marked resemblances with the structure of both crystalline and fibrous protein, but the virus structure does not belong to any of the classes hitherto studied. There are indications that the inner structure is of a simpler character than that of the molecules of crystalline proteins. (Bernal and Fankuchen :1941abc:163)

Finally they recorded that virus particles appeared to be shorter inside the plant than those outside, and that the bushy stunt viruses were probably spherical.

6 THE CYCLOL HYPOTHESIS AND THE REACTIONS OF THE CRYSTALLOGRAPHERS

6.1 Introduction

The cyclol theory of protein structure was proposed by Dorothy Wrinch in 1936 as a working hypothesis, and became the focus of a very bitter public debate in the community of crystallographers and protein chemists in the late thirties and early fourties.

Wrinch was an Oxford mathematician friendly with many of those interested in the structure of proteins, including many of the crystallographers. She was especially friendly with Dorothy Hodgkin (Hodgkin :1970a:12) and she was a member of the "Theoretical Biology Club".

In the thirties the structure of globular proteins, which was unknown or only guessed at, was the object of work of scientists from a number of different backgrounds. Physical chemists such as Svedberg started measuring the molecular weights of proteins in the late twenties. Surface chemists were studying their properties, and biochemists, especially at Cambridge and in the USA were carrying out degradations in order to determine the amino-acid composition of the proteins. As has been described in the two previous chapters, the crystallographers were making important contributions through the work of Bernal and Astbury. This cross disciplinary "protein community" is more fully discussed in Chapter Eight.

Although the polypeptide theory of protein structure was fairly well established, none the less some crystallographers were hedging their bets (Hodgkin :1970a:14). There was a great deal of published and unpublished speculation about the structure of the proteins. Two theories in particular were very well known:

(1) The theory of the molecular weight classes was devised by Svedberg, who argued that most proteins fell into certain classes in terms of their molecular weights (the fundamental unit being about 34,500).

(2) The theory advanced by Bergmann and Niemann, two American biochemists, who made claims about the frequency and order of amino-acids in proteins. This theory has been briefly mentioned in previous chapters. The Wrinch theory of the cyclol was a further theory of protein structure, although it had more revolutionary implications for several disciplines than the other two.

Each of the three theories finally became unacceptable to the great majority of those concerned, and yet, for a time, they formed a mutually supportive theoretical structure. To say this is not to say that it was necessary to believe in all three. It was possible to adhere to any one or two; the best supported of the three was the fairly low level generalisation advanced by Svedberg. It seems that most workers on proteins during the thirties accepted that molecular weights did fall into classes, although the significance to be attached to this was not immediately apparent, and even here, the theory was never entirely snag-free. The Bergmann-Niemann hypothesis was open to the objection, raised by Astbury among others, that a single position on the amino-acid chain might be occupied by more than one amino-acid residue.

The least acceptable was the Wrinch cyclol hypothesis which resulted in controversy on two main fronts. First, there was debate about the theory itself -- were proteins in fact built in the proposed manner? Secondly, there was the debate about Wrinch's interpretation of crystallographic data. She suggested that the data supported the cyclol theory, while her opponents argued that she was making use of

incorrect crystallographic techniques. Thus there was controversy on two fronts -- protein theory and crystallographic methods. While the two were connected, it is the latter that is of primary concern here.

6.2 The Cyclol Hypothesis

In March, 1936, Wrinch published a paper in Nature in which she advanced a working hypothesis concerning the nature of proteins (Wrinch :1936a). She wrote as follows:

Any theory as to the structure of the molecule of simple native protein must take account of a number of facts, including the following:

- (1) The molecules are largely, if not entirely, made up of amino acid residues. They contain -NH-CO linkages, but in general few -NH₂ groups not belonging to side chains, and in some cases possibly none.
- (2) There is a general uniformity among proteins of widely different chemical constitution which suggests a simple general plan in the arrangement of the amino acid residues, characteristic of proteins in general. Protein crystals possess high, general trigonal, symmetry.
- (3) Many native proteins are "globular" in form.
- (4) A number of proteins of widely different chemical constitution split up into molecules of submultiple molecular weights in a sufficiently alkaline medium.

The facts cited suggest that native protein may contain closed, as opposed to open, polypeptides, that the polypeptides, open or closed, are in a folded state, and that the type of folding must be such as to imply the possibility of regular and orderly arrangements of hundreds of residues.

An examination of the geometrical nature of polypeptide chains shows that, since all amino acids known to occur in proteins are α - derivatives, they may be folded in hexagonal arrays. Closed polypeptide chains consisting of 2, 6, 18, 42, 66, 90, 114, 138, 162 ... ($18 + 24n$) ... residues form a series with threefold central symmetry. A companion series consisting of 10, 26, 42, 58, 74, 90, 106, 122 ... ($10 + 16n$) ... residues have twofold central symmetry. There is also a series with sixfold central symmetry: others with no central symmetry. (Wrinch :1936a:411)

This pattern permitted hundreds of amino-acids to exist in an orderly array in a manner that was both simple and uniform, thereby complying with many chemical observations. A transformation linking CO and NH groups would create cage structures (See Figure 7)! All the side-chains would project from a single sheet of the proposed cyclols, thus leaving the other side free. A true protein monolayer of this form would have an area of 9.9\AA^2 per amino-acid. Several layers might lie on top of one another, connected by cytosine and hydroxyl bridges, and as there would be plenty of room for water in such a structure the hydration properties of many proteins would be explained. Since alternate layers in a protein would be held together by hydroxyls, these would be very sensitive to alkaline solutions, and would split thus liberating the separate layers. She noted that:

Svedberg's results, according to which a number of different native proteins break up into smaller molecules with sub-multiple molecular weights, here find a simple interpretation. (Wrinch :1936a:412)

She suggested that this theory accounted for the four classes of data mentioned above, and she noted that it was similar to Astbury's 1931 structure of - keratin in which one CO and NH group in every three was cyclised. Finally, she cited further facts from organic chemistry, X-ray analysis, enzyme chemistry, and cytology, which she found suggestive in relation to the theory. There were:

- (1) The rhythm of 18 found in the distribution of amino acids in gelatin (Bergmann).
- (2) The low molecular weight for most material from which lactalbumin is formed (Svedberg).
- (3) The case of secretin, a protein with a molecular weight of 5,000, with no open polypeptide chains (Hammersten).

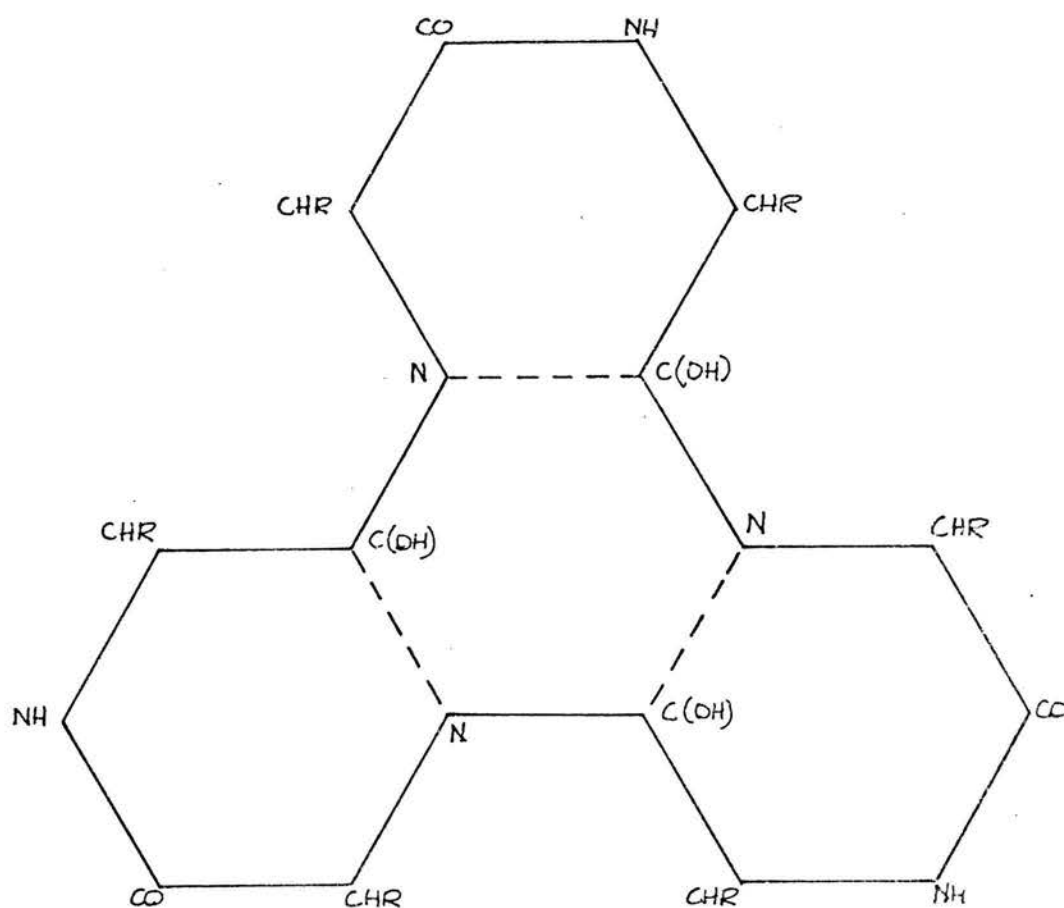
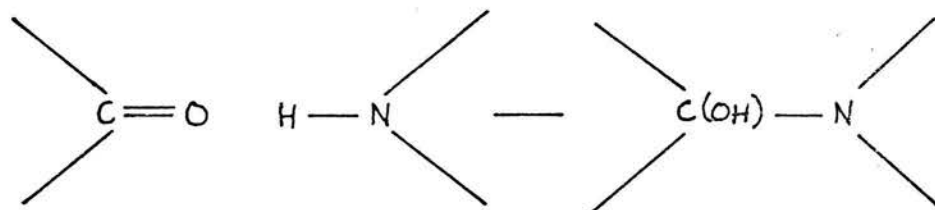
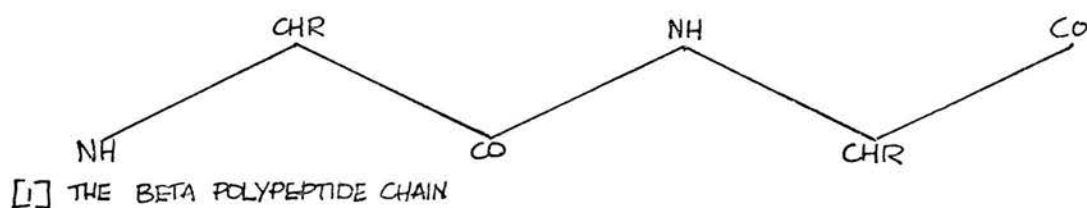


FIGURE 7 THE CYCLOL MOLECULE AND THE TRANSFORMATION

(4) The nuclear membrane which was known to play an important part in mitosis.

(5) The fact that the dipeptide substrate in dipeptidase was known to have a hexagonal configuration (Bergmann).

(6) The possibility that immunological reactions would depend not only on amino-acid composition but also on position.

Later in the same year Wrinch published a second letter in Nature (Wrinch :1936b) in which she discussed the energy of formation of the cyclol molecules. In a third paper (Wrinch :1936c) she discussed some physiological implications of the theory, and in a fourth paper written jointly with Dorothy Jordan Lloyd, the protein chemist (Wrinch and Jordan Lloyd :1936) she developed the idea in relation to the hydrogen bond. Reviewing the progress of the idea up to that point, she pointed out that the cyclols did not have to be restricted to hydroxyl bonds, but could be built out of Hydrogen bonds. In 1932 Jordan Lloyd had suggested that hydrogen bonds were important in proteins, and other writers, including Mirsky and Pauling had more recently developed the idea.

In the following year Wrinch wrote several more papers including two that were published in the Proceedings of the Royal Society (Wrinch :1937a; 1937b). In the first of these she developed the notion of the "space enclosing" cyclols. One set of enclosing cyclols was developed in detail, as it appeared to fit data related to the behaviour of proteins in solution, and the reversible association and hydration of protein molecules. This was the $C_1, C_2, \dots C_n$ series comprising 72, 288 ..., $72n^2$ residues. She wrote:

It is found that the molecular weights of proteins are not distributed at random, but fall into a sequence of widely separated classes, the molecular weights in one class

varying by as much as 20% from a mean value. This we interpret to mean that the proteins falling into one of these classes have a common structure as regards the arrangement of the constituent amino acids, and we suggest that each class connotes one closed cyclol network or an association of a certain number of such units. The variation in molecular weight within a class is then accounted for by the different selections of residues in the various proteins.... (Wrinch :1937a:520)

She then went on to make some predictions about the structures and average residue weights of several proteins. In the case of insulin the C_2 molecule fitted the calculated unit cell.

Finally she added a note about the new work by Bergmann and Niemann, in which they put forward the $2^n 3^m$ hypothesis. She wrote:

These results are immediately relevant to the implications of the cyclol theory, which readily interprets the total numbers of amino-acid residues per molecule, without the introduction of any ad hoc hypothesis.

In claiming that 288 is the number in the molecule of egg albumin, the work confirms, for this protein, the prediction, made in October 1936, that the proteins whose molecular weights are in the neighbourhood of 35,000 are polycondensation products comprising 288 units

In claiming that the number of residues in cattle fibrin and cattle haemoglobin is 576 per molecule, the work confirms for these proteins the suggestion that some of the proteins in the 70,000 class have 576 residues per molecule. (Wrinch :1937a:521)

Initial work on insulin X-ray data was also mentioned in a paper published in Science in 1937 (Wrinch :1937c). Symmetry considerations were found to be consistent with the X-ray data, and as was mentioned above, the C_2 molecule was seen to fit "easily and elegantly" into the unit cell.

6.3 Patterson Projections and the Cyclol Theory

Wrinch and Langmuir argued in 1938 (Langmuir and Wrinch :1938a) that the Patterson vector diagrams of insulin calculated by Hodgkin

were compatible with the C_2 cyclo1 structure. In addition they advanced a "geometrical method" which suggested that a vector map could be constructed from certain configurations of atomic reflecting centres so long as these were point sources. This method was further expounded in November, 1938, (Wrinch :1938a) when Wrinch discussed the nature of the phase problem and pointed out that the Patterson method made use of the intensities only. She noted that the Patterson function, which represented:

... (... the weighted distribution of density in the crystal about any point) can be used in conjunction with any structure already proposed, to pass it for further consideration or to reject it, according as its vector function does or does not tally with it. (Wrinch :1938a:955)

There was one problem with the Patterson method: for any given vector expression there might be more than one possible electron density distribution which would satisfy the conditions. The "geometrical" method had been developed to avoid this problem. She noted that;

This new method entirely alters the situation regarding the possibility of using vector maps to discover the atomic structure of crystals. (Wrinch :1938a:955)

From a study of the insulin vector distribution she argued that there were only two possible electron distributions. One of these was ruled out by the intensities of the peaks in the vector projection. Her description of the geometrical method was brief:

It bears to the customary approach the same relation as the quantum theory of light bears to the classical theory, picturing a crystal as a point intensity distribution in atomic space S_1 , corresponding to which there is a second easily derivable point intensity distribution in vector space S_2 , which may be compared with the experimentally obtained vector maps already discussed. (Wrinch :1938a:955)

She concluded this paper by noting that further work was in hand, and that the method was being used to determine in greater detail,

information concerning the structure of crystalline insulin.

Prof. E.H. Neville of the University of Reading, whom Wrinch had acknowledged in the above paper, contributed to the discussion (Neville :1938). He noted:

(It has been argued) that every vector series must be common to an infinity of atomic structures, and we must accept the depressing conclusion that although an immense amount of toil has been devoted to collecting intensity observations and constructing vector diagrams for actual substances, this toil and the ingenuity and patience which have been needed for the discovery of structures compatible with the diagrams have alike been wasted, since the probability that a particular structure found in this way is the correct one remains in any event negligibly small. (Neville :1938:994)

He went on:

Dr. Wrinch is undoubtedly right: the Patterson diagrams contain far more information than was suspected before she began to study the published insulin diagrams for herself. In fact, reconstruction of a discrete point-set from its vector map is a systematic process. At various stages alternatives must be examined, but the analysis is exhaustive.... There are no parameters in the solutions. The notion that the atomic structure remains hopelessly indeterminate however thoroughly the vector analysis is carried out is quite untenable; it is obviously absurd in the simplest cases, and gains nothing in plausibility when the map is complicated.... (Neville :1938:994)

He argued that this mistake arose because it was not realised that stringent criteria must be followed if the Fourier series was to correspond to a point set. If the coefficients in the Fourier series varied while the vector series remained unchanged, it was not the atomic structure that varied, but rather the clarity with which the Fourier series represented such a structure that was lost.

He went on to discuss the fact that it was impossible to discover all the components of the Patterson series by experiment; similarly, however, he noted that it was impossible to consider all the points in real space. By dealing with the most important intensities and the most important points, it should be possible to derive an

adequately reliable vector map, and then the main points in real space. "The problem" he noted, on obtaining a vector map became "one for the mathematician, whose verdict on the evidence is final".

6.4 The Controversy

In three letters published simultaneously in Nature on January 14th, 1939, W.L. Bragg, Bernal and J.M. Robertson all strongly rejected the geometrical method. Taking them in order, Bragg (Bragg, W.L. :1939a) wrote:

Letters on the interpretation of Patterson Fourier syntheses (vector maps) have recently appeared in Nature. Is not the claim made or implied in these letters, that a new method of interpretation has been discovered, due to a misapprehension concerning the existing methods of crystal analysis? (Bragg, W.L. :1939a:73)

He outlined what he described as the "classical method" of crystal structure analysis, which roughly corresponded to the "trial and error" method. Then he went on:

In the second paragraph of his letter, Prof. E.H. Neville outlines an argument which purports to demonstrate that substantial reconstruction of the crystal structure is theoretically impossible, since the observations may correspond to an infinity of solutions, and then proceeds to combat this view. I do not know from what source he got the impression that such a view has ever been expressed or could possibly be held by anyone who is acquainted with the methods of crystal analysis. If the distribution of scattering matter within the unit cell could have any general form, the problem would of course be indeterminate; but in actual fact we know the scattering matter to be clustered in a characteristic way around a finite number of atomic centres; this makes the solution unique. (Bragg, W.L. :1939a:73)

Bragg then briefly described Fourier methods and some uses of the Patterson vector method. He mentioned the fact that in the case of a crystal with a centre of symmetry the phase angles in the Fourier series would either be plus or minus one, and he noted that a common way of proceeding in the case of centrosymmetric molecules was to determine

a first approximation to the structure by trial and error, in order to reveal the signs of the more important reflections. Patterson diagrams had also been successfully used to determine molecular structures where there were one or two outstandingly heavy atoms $\pm\pm$ in this situation it was relatively easy to locate these atoms from the Patterson diagram. He went on:

These heavy atoms are so important in fixing the signs of the Fourier terms that the analysis can then be completed. The "geometrical method" proposed by Wrinch, which Prof. Neville claims "has opened a new chapter in crystal analysis", is essentially the same as that used in these and other investigations. (Bragg, W.L. :1939a:73)

Bragg then went on to underline the extreme difficulty of adequately interpreting Patterson diagrams, pointing out that insulin, the case in point, was many more times complicated than the simple organic molecules on which it had previously been used. He wrote:

I would not venture to suggest that analysis is a hopeless task; on the contrary, there is every hope of ultimate success I would plead, however, for a due sense of proportion. Langmuir and Wrinch claim that the main features of the Crowfoot diagram can be explained by a certain concentration of scattering matter in a simple way at a few typical points in the molecule. If this claim is substantiated, it affords a useful hint as to one possible solution; but whether it is unique depends, as in all cases of X-ray analysis, on the justification for the assumptions which are made. In simple structures, we are on sure ground, for we know the scattering units to be a finite number of atoms. In a protein, the assumptions must as yet be vague and provisional. Exaggerated claims as to the novelty of the geometrical method of approach and the certainty with which a proposed detailed model is confirmed are only too likely, at this stage, to bring discredit upon the patient work which has placed the analysis of simpler structures on a sure foundation. (Bragg, W.L. :1939:74)

Bernal's letter dealt less with methods of X-ray analysis in general, and more with the case of insulin, and the nature of the evidence supporting the cyclol cage structure proposed by Wrinch (Bernal :1939b). Firstly he noted that in essence, the method

proposed by Wrinch and Neville was in no way new. Next he noted that one basic assumption -- that the scattering matter was at points, rather than distributed throughout the crystal -- that was at least questionable. Even if this was ignored, however, there was still greater ambiguity in Wrinch's papers than might be supposed.

He next argued that there were two ways of attempted to proceed in relation to Patterson diagrams. The first of these was to elucidate the maximum information from the available diagrams (in this case insulin). Bernal wrote of this that it:

leads to a family of solutions obtainable by attributing different weights to the seven symmetrically distinct points in a hexagonal packing of two layers. A large number of these give no worse fits than the particular case which Dr. Wrinch claims as the unique solution. None of them, however, gives a complete fit, and to discriminate between them would appear, for lack of further experimental evidence, to present considerable difficulties. (Bernal :1939b:74)

The second method was to attempt to account for the observed pattern by means of an a priori model. This had often been done with simple molecules in the past. However, its success depended on choosing a plausible structure on the basis of chemical knowledge. He doubted the Wrinch model on two grounds. Firstly several protein chemists had suggested that it was open to "grave doubts" for chemical reasons. Secondly, even if the amino-acid residues did link in four ways instead of two as in the conventional theory, Wrinch had by no means covered all the possible structures that would result.

Bernal then turned to the actual method by which the vector distribution had been calculated, and here he was really scathing:

Vector maps of Dr. Wrinch's hypothetical cyclol structure bear no resemblance to those which have been derived by Miss Crowfoot from her observations. The distribution of atoms in the cyclol skeleton is far too continuous to give rise to any definite peaks, and no distribution of side chains can do other than increase the blurring of the

picture. Dr. Wrinch has not however used the vector map of the cyclol skeleton. Instead of this, she has chosen certain density concentrations, which are treated as positive and negative point scattering centres, for the construction of the vector diagrams. It is difficult to see on what principle in relation to the structure these centres have been chosen. Two of the strongest of them are completely arbitrary and another is attributed to a zinc atom the 28 electrons of which would scarcely seem effective scattering centres in a molecule with 20,000 electrons. (Bernal :1939b:74)

Even if the selected points led to the observed Patterson diagram, this would at most suggest that the proposed scattering centres existed although they might have a physical structure totally different from the one proposed. In fact, in the case of this work, it would not even be that suggestive. Wrinch had chosen a minute and arbitrary number of vectors (thirteen) from a total of 3,600 which would be provided for in the model. She suggested that this omission made no difference to the projection, but Bernal contested this strongly. There was no evidence that the cyclol model explained the Patterson projection data, and in fact Bernal suggested that the cyclol molecule would produce a projection incompatible with that actually observed. He did not advance a model of his own, suggesting that the problem remained an open one, however, disappointing this was. He hoped that this fact might lead to renewed collaboration between physicists and chemists in an attack on the structure of the proteins.

Robertson (:1939) also questioned certain of Wrinch's assumptions about the scattering centres, while in addition pointing out that:

It is quite obvious that fifty-nine relative measurements of amplitude cannot define a structure consisting of several thousand atoms. So far as these measurements go, the structure is effectively a continuous distribution of scattering matter, and every arbitrary assignment of phase constants to the amplitudes will yield a solution. (Robertson :1939:75)

He considered that the Patterson method had not proved very successful in the field of organic structure determination. In his view the

heavy atom method was likely to prove more powerful. He noted, prophetically:

It may be going too far to suggest that the insulin structure would be determined in this way. The molecule does, however, contain a few zinc atoms, and if these could be replaced by mercury, as has been suggested, a very profitable study might ensue. (Robertson :1939:76)

In view of this rather strong response from three important crystallographers, there is a touch of irony about the opening sentence of a paper published by Wrinch and Langmuir (Langmuir and Wrinch :1939a) in the same edition of Nature. They wrote:

The confirmation by X-ray data of C_2 , the 288-residue cage structure proposed for the insulin molecule, makes it of interest to consider the nature of the cyclol bond.... (Langmuir and Wrinch :1939a:49)

Another communication to Nature from Wrinch was published in March. Although this was mainly devoted to a discussion of chemical criticism of the cyclol theory (Wrinch :1939a:483), she also mentioned the doubt that had been cast on the validity of the Patterson X-ray data, on the adequacy of the X-ray data, and on the possibility of making any deductions from such data. In view of this she felt that any conclusion on this particular point would have to be postponed.

In April, 1939, Riley and Fankuchen published a paper in Nature in which they constructed a derived Patterson vector diagram for the skeleton of the cyclol C_2 molecule (Riley and Fankuchen :1939). They did this by considering all the carbon and nitrogen atoms on the skeleton of the cyclol while ignoring all the side chains, arguing that this omission would not drastically affect the nature of the Patterson projection. They came to the following conclusions:

(1) The cyclol fabric cannot adequately be represented by the set of equivalent masses chosen by Wrinch and Langmuir.

(2) Even if this representation were correct, the vector maps obtained from these equivalent points do not fit the experimental data if all the vectors are taken into account (Bernal :1939b)

(3) The vector map derived from a consideration of the atomic skeletons of the cyclol molecules in the unit-cell does not fit the Patterson analysis of insulin as found experimentally by Crowfoot.

It can consequently no longer properly be claimed that the X-ray evidence furnishes any direct confirmation of the cyclol structure proposed for insulin. (Riley and Fankuchen :1939:649)

Within a couple of months Wrinch was in print again. (Wrinch :1939b) After contrasting a couple of contradictory statements made by Bernal and Crowfoot respectively, about the vector distribution that would be derived from a cyclol C_2 molecule, she examined the paper by Riley and Fankuchen discussed above. The Patterson map constructed by Riley and Fankuchen had been used:

to disprove two propositions, neither of which to my knowledge has been asserted, namely, (1) the insulin molecule consists of these 288(C-N-N) units, and (2) these units and six points at the corners of a C_2 skeleton have the same vector map. This map cannot be regarded as a contribution to the study of insulin, since chemical requirements alone dispose of any idea that the insulin molecule has the composition (C-N-N)₂₈₈. However, the authors claim that it disproves also the hypothesis that insulin is a C_2 structure consisting 288 ((C(OH)CHR)-N) units. (Wrinch :1939b:763)

Far too many assumptions had been made to allow to any valid assertions to follow. The most important assumption was that the amino-acid side chains would have no important effect on the structure of the Patterson projection. A second was the fact that arbitrary reflecting values were ascribed to groups of unknown chemical composition. Wrinch concluded by mentioning Robertson's letter (Robertson :1939) and agreeing with his view that it was better not to make guesses about protein structures until the data were improved. The exception was that unit cell, molecular size, and molecular weight could be determined and these were in good accord with a Cyclol C_{288} cage structure.

In May, Bernal, Fankuchen and Riley published a further brief letter in Nature in answer to the above. (Bernal, Fankuchen and Riley :1939) First, they noted that no one imagined that insulin contained only (CCN) groups, but as these were the only groups whose positions were given by Wrinch, they were the only ones on which the calculation could be based. They went on:

Dr. Wrinch is, of course, at liberty to place other concentrations of density wherever she likes, but she cannot logically claim in this case that the structure arrived at in this way offers any confirmation of the cyclol hypothesis. (Bernal, Fankuchen and Riley :1939:897)

They also considered her claim that the unit cell fitted with the proposed cyclol structure, and they concluded that:

Any spherical molecule of approximately the right molecular weight would fit the cell equally well. The only positive agreement is in the presence of a trigonal axis of symmetry, which can scarcely be claimed to justify the acceptance of such an elaborate construction. (Bernal, Fankuchen and Riley :1939:897)

Once more they repeated their assertion that the X-ray evidence, rather than supporting the cyclol theory, tended to undermine it. Finally they noted that the arguments against the cyclol theory had been very fully stated, and they felt it unprofitable to continue the discussion until further evidence became available.

Indeed, this appears to be the last time that any British crystallographer took issue with Wrinch in public, although she wrote several more letters to Nature, one of which purported to refute the argument in the above letter by Bernal, Fankuchen and Riley (Wrinch :1940a). During the period of the controversy, Wrinch had moved from Oxford to the USA, and in 1940 she was at the Johns Hopkins Department of Chemistry. Fankuchen had also, of course, returned to the States with the outbreak of war, and Bernal had been drafted into war work.

However, Wrinch advocated the cyclol theory until 1947 at least, when she proposed a cyclol structure for insulin on the basis of a three dimensional vector map (Wrinch :1947). By this stage very few crystallographers and protein chemists believed in the theory.

Perutz has recently noted:

I took no published part in the controversy, but I was convinced on general chemical grounds that it was wrong. It required a chemical transformation of the polypeptide chains involving carbonyl groups that I regarded as extremely unlikely. She was supported by Irving Langmuir, who was a physicist, and did not know any organic chemistry. All X-ray crystallographers and organic chemists were opposed to the hypothesis. Wrinch was irrationally attached to the hypothesis, and was unable to abandon it -- she is one of those tragic figures in science. (Perutz :1970b:3)

Hodgkin, who is still friendly with Wrinch, recently noted in similar but rather kinder language:

It is a pity she became so devoted to (the cyclol theory), and I think that this devotion came from the aesthetic beauty of the theory. Anything so beautiful, she felt, had to be right, and it seemed to her that her ideas fitted the data so well, that it made it very difficult to see the evidence against them. (Hodgkin :1970a:12)

6.5 Conclusion

The above account suggests that not just protein but other crystallographers were involved in a major published controversy concerning the cyclol theory. The reasons for this involvement were as much concern with technical details of interpretation of X-ray data, as with concern about the nature of the theory itself. Robertson and Bragg restricted their remarks strictly to the technical problems involved. Bernal, Hodgkin, Riley and Fankuchen were more outspoken in their opposition to the cyclol structure, but they too concentrated their attack very much on points of technique, and particularly the "geometrical method". Only Astbury, whose very

brief published contribution to the debate has not been mentioned, can be seen as raising objections that were primarily chemical rather than crystallographic.

7 TECHNICAL PROBLEMS IN PROTEIN CRYSTALLOGRAPHY IN THE THIRTIES

7.1 Introduction

In this section the main problems confronting the protein crystallographers in the thirties will be discussed. Some of them have already been mentioned in preceding chapters, but as a background to a discussion on attitudes to protein crystallography, a more systematic account is required.

7.2 Technical Problems

7.21 Preparation of Satisfactory Crystals

One of the main problems in crystallography, and protein crystallography in particular, was, and still is, the preparation of satisfactory crystals. Astbury faced a problem of this sort in his work on keratin, a protein that was by its nature incompletely crystalline. The early workers who studied the globular proteins obtained very inferior diffraction pictures, and it was not until Bernal's work on pepsin in 1934 that good single crystal protein X-ray diffraction photographs were obtained. This work has been discussed above, and will not be further considered here (Bernal and Crowfoot: 1934).

The work by Bernal gave X-ray photographs which were potentially capable of revealing atomic detail. This removed a very important technical bottleneck, but it did not mean that the process of X-ray photography of proteins became an easy one. In many cases crystals were difficult to obtain, and temperamental when handled. Thus, one of the main reasons why Kendrew worked on the myoglobin of sea animals was that good myoglobin crystals were easily obtained from seal and whale flesh (Kendrew :1970a).

Another problem emerged later with the development of the heavy atom method. This concerned the production of crystals with heavy atom replacements, but it was not a problem that seriously affected workers in the thirties.

7.22 The Phase Problem

Phase determination is the key problem in all X-ray crystallography. If the crystals have a centre of symmetry then it is normally quite easy to determine the phase angles --they are either plus or minus one. If the crystals have no centre of symmetry, and most do not, then it is necessary to calculate the phase angles by other means. In the early days the methods were usually those of trial-and-error. If a reasonable guess of the structure was made, then a first approximation to the phase angles could be established. From this guess the structure could be refined.

One possible way round the phase problem was the "Patterson method" which made use of intensities rather than phase angles in the Fourier series. However, as can be seen from the account of the cyclol controversy, vector diagrams of this sort were not readily interpretable where the molecule was complicated.

Another way round the problem that was much discussed in the late thirties was the "swelling and shrinking method". This was one of the two methods mentioned by Bernal in a 1939 lecture to the Royal Institution (Bernal :1939c:665). If X-ray pictures of proteins at various stages of hydration were obtained then the intensities of the reflections would change, but hopefully it would be possible to construct Patterson projections that would lead, by comparison, to location of some of the more important atomic scattering centres. This was a hope that proved to be ill-

founded:

I spent some time working on this, but there were various problems, one of which was that the amplitude values needed to be large. I now know that even had we been successful we would have achieved no unique solution. In the third dimension the features would have been superimposed upon one another in an insoluble manner. So I stopped working on that at an early stage. (Perutz :1970b:3)

In fact with various refinements, this method was still being used as late as 1954, although with very limited success (Bragg W.L. :1965c:8ff).

The other method mentioned by Bernal, the "heavy atom method", was fairly well known in crystallography in the thirties. Though it had been at the back of crystallographers' minds for years, J.M. Robertson in the middle thirties was the first worker to develop it systematically. He wrote a classic series of papers (Robertson :1935; 1936; 1937; 1940) in which he explored the potentialities of the method in relation to a series of organic molecules, the phthalocyanines.

The heavy atom method, like the swelling and shrinking method, is a way of determining the phase angles of the reflections. Technically speaking, there are in fact two different methods, the isomorphous replacement technique, and the heavy atom technique. The isomorphous replacement technique is a method that involves comparing the reflections from two crystals that are isomorphous and yet contain different heavy atoms at certain points. The phase contributions of the different atoms may be determined by comparing the diffracted intensities. Knowing the theoretical scattering curve of the atoms concerned, the phases of the reflections in general can then be calculated. In the case of the heavy atom technique, the heavy atom is assumed to dominate the phases of the

reflections and the contributions of the other atoms are ignored in the first instance. The structure is then refined by successive approximation.

In 1939 both Robertson and Bernal suggested that the isomorphous replacement method might be used to determine the structure of proteins, but this in fact was not done for another fifteen years. There were two main reasons for this. Firstly, the chemical problems involved in making heavy atom replacements were considerable. Secondly, and more relevant to the late thirties, protein crystallographers were pessimistic about whether the method would work for molecules as large as proteins. Thus, Hodgkin has noted:

the intensity changes produced by replacing zinc with cadmium in insulin proved too small to measure on our early X-ray photographs, and we began to discuss with insulin chemists how to get heavier atoms into insulin. Experiments on the iodination of insulin had already been carried out; it seemed that these should be followed up. Meanwhile, the report of the preparation of pale yellow crystals of iodobenzene-azo-insulin by Reiner and Lang came into our hands. Dr. Reiner very kindly sent us samples of a few milligrams of very tiny crystals from which it was just possible to grow slightly larger crystals and to record a few spectra. These were enough to indicate that the crystal lattice was essentially unchanged as were the relative intensities of the inner strong X-ray reflections. (Hodgkin and Riley :1968:25)

These experiments were carried out in 1941. Hodgkin notes that although she intended to repeat the experiments at a later date with a higher iodine content "somehow we never did". One reason for this was that Reiner thought that the iodine would be scattered at the different tyrosine sites throughout the molecule. She goes on:

our crystals were too small and our methods of measurement too weak to have recorded at that time the effects for which we sought. Perhaps it was just as well that our somewhat pessimistic comments were buried in our notebooks and reports. (Hodgkin and Riley :1968:25)

Part of the pessimism arose from concern with the strength of

the X-ray reflections from protein crystals. Although it was realised that protein crystals gave, volume for volume, relatively weaker reflections than smaller crystals, it was not realised just how weak they were. This emerged as a result of work by A.J.C. Wilson, E.W.Hughes, and D.Harker from about 1942 onwards. The weakness was important because it meant that heavy atoms were more powerful in phase angle determination than was thought at the time, and as a result, the method was more appropriate to proteins. The isomorphous technique was not applied to haemoglobin and myoglobin until 1954, although other developments --the isomorphous replacement work by Bijvoet, for example-- built up a background from which work on the proteins could be successfully launched.

7.23 The Problem of Measuring Large Numbers of Intensities

During the cyclol controversy J.M.Robertson indicated the absurdity of trying to locate thousands of atoms with relatively few intensity measurements. This was a graphic way of describing a general problem, in part related to the sheer number of reflections, and in part to the problems of accurate intensity measurement. Kendrew tackled this problem in the fifties when he developed the optical densiometer. At a later date Phillips and Arndt developed automatic diffractometers.

7.24 The Problem of Data Handling

In the protein heavy atom work the problem of handling the data and calculating the necessary Fourier series became enormous. Although various short methods of calculation were developed in the thirties (the most widespread being the Beevers-Lipson strips) the basic problem was not tackled until the late fourties. Even then there were few workers --notably Kendrew and Bernal-- who had any real idea

of the size of the computation problem. It was recorded in Chapter Three that Kendrew's work in this area encountered a certain amount of resistance from Bragg and Perutz who preferred to use Hollerith card machines.

7.25 Interpretation of Electron Density Maps

Another problem which troubled the workers in the later thirties and forties turned out to be illusory. Hodgkin has recently written:

... the spacing of the spectra you get from a protein is too large to permit the resolution of individual atoms, and in determining a structure, you are really only safe if you can place the individual atoms. This comes out in the correspondence in Nature in 1939, where Bernal, Bragg and J.M. Robertson are arguing against Wrinch and Langmuir, who said that the cyclol theory fitted the insulin Patterson projection so well. Bragg, who took what you might call the main line, argued that **you** only knew that a structure was correct when you could place all the atomic positions. So the question was, when one got a final electron density map, would one know what it meant? In fact, with the accumulated experience of the years, we were able to determine structures from partly resolved maps. In fact it has surprised even those who were most involved in it, how unambiguous the maps have turned out to be. They have turned out to be more interpretable than we would ever have dared to hope.

(Hodgkin :1970a:8)

This was partly because by the time accurate model building was required, the measurements of many crucial components in the proteins were known. Thus, with a knowledge of the structure of the α -helix (Pauling, Corey and Branson :1951) parts of the interior of the myoglobin and haemoglobin molecules were easily interpreted when 6.0 Å. maps became available. In addition, knowledge of the structures of the amino-acids also became important.

7.3 Conclusion

In 1939 the problems in protein crystallography were immense. Admittedly, they did not all turn out to be real, and some were not fully understood at the time. None the less it is not surprising that some were pessimistic about the outcome of work on protein X-ray

crystallography, and did not work in the area themselves. The problems mentioned above were all massive and had to be solved (or shown to be illusory) before the structure of any crystalline protein could be determined.

8 THE "PROTEIN COMMUNITY" AND ATTITUDES TO PROTEIN X-RAY CRYSTALLOGRAPHY IN THE LATE THIRTIES

8.1 Summary

In this chapter a number of propositions will be argued. They are as follows:

8.11 The "Protein Community"

The term "protein community" will be introduced and defined as that group of scientists, from whatever disciplinary background, who were interested in the structure, chemical and genetical properties of proteins in the thirties, who took part in cross-disciplinary discussions on the subject. It will be suggested that communication between such scientists was at a fairly high level in the late thirties. It will not, however, be argued that they were all in communication with one another, and indeed it is possible that the specifically genetical component of the protein community was to some extent distinct from the rest of the community. Several of the protein crystallographers were active in the interdisciplinary discussions of the protein community.

8.12 Attitudes to Protein Crystallography

A number of attitudes to the work of the protein X-ray crystallographers in the late thirties will be discussed, although they are not in all cases completely clear nor mutually exclusive. They can be divided into the following headings:

8.121 Direct Approach: Perutz

The direct assault was expressed primarily through the work of Perutz and Kendrew. They believed that it was by crystallographic methods alone that the structure of the proteins would be solved.

They also thought that whole proteins, rather than their constituent parts should be the object of study.

8.122 Direct Approach: Hodgkin

Hodgkin argued that the development of techniques by the study of simpler molecules was necessary, or at least advisable. This was also a purely crystallographic approach, owing little to protein chemistry and other disciplines.

8.123 Direct Approach: Bernal

Bernal held that a direct crystallographic approach to the proteins was also possible, but he coupled this with a belief that certain methods --notably computing and photography-- would have to be developed if proteins were to be successfully structured. This was most clearly expressed by Bernal after the Second World War. In the earlier period, although advocating a frontal crystallographic assault, he also emphasised the importance of cross-disciplinary collaboration.

8.124 Indirect Approach: Pauling

Pauling argued that the way to make progress in protein structure determination was to undertake crystallographic studies of component parts --for example of amino-acids. From a study of bond angles and structural chemical considerations, it might then be possible to build plausible models of the proteins. This constituted a crystallographic and structural-chemical approach.

8.125 Composite Approach: Astbury

Astbury used data from whatever source in order to develop theories about protein structure, and X-ray crystallography was only one of several important sources of data. This attitude was also expressed by Bernal in the late thirties, although there is less

evidence of this approach in his published papers which were more exclusively crystallographic.

8.126 Other Crystallographic Attitudes

A number of non-protein X-ray crystallographers felt that proteins were so complex, and the technical problems were of such magnitude, that it was better to work on simpler molecules. Others, however, though they took no part in the work themselves, were more optimistic and offered encouragement.

8.127 Attitudes of Non-Crystallographers

No systematic survey of these attitudes is made, but a couple of instances which suggest that some importance was attached to protein X-ray crystallography, are mentioned.

8.2 The Protein Community

Scientists from a number of different disciplinary backgrounds became interested in the structure, chemical, and genetical properties of proteins in the twenties and thirties, and this resulted in a considerable amount of cross-disciplinary communication. The "protein community" is defined as that group of scientists who were interested in proteins from the structural, chemical and genetical points of view, who were in contact with scientists from other disciplinary backgrounds who were also interested in such questions.

Such communities, or social circles, exist in many areas of science. In the case of the protein community intercommunication was at a particularly high level during the middle and late thirties. No comparative evidence is offered to support this assertion, but none the less from impressionistic historical data the existence of such a community can be deduced. The matter of concern is not so

much the extent of the community itself, but the fact that a number of X-ray crystallographers can justly be described as having been members of it.

8.21 Evidence Concerning the Protein Community

In the spring of 1938 a small meeting was held at Klampenborg in Denmark. This was a cross-disciplinary gathering concerned with genetics at a molecular level. The members of this group are listed in Figure 8, Members of the Klampenborg Conference, 1938. At this time it was thought that the genetic material was either a protein, or a combination of protein and nucleic acid. For this reason much of the discussion centred around the structure of proteins. Waddington wrote of this meeting that:

Physics was represented not only by Quantum theory men such as Auger and Zimmer, but by X-ray crystallographers such as Astbury and Bernal; this was the first time that there was a real meeting of geneticists and crystallographers.

(Waddington :1969:318)

In the summer of 1938 the Cold Spring Harbor Symposium on Quantitative Biology was on the subject of protein chemistry. Although the number of people who attended is too large to list (Cold Spring Harbor :1938:vii) it included workers from Departments of Physiology, Chemistry, Zoology, Medicine, Agriculture, Botany, Biochemistry, Physical Chemistry, Pharmacology and Bacteriology. The British contingent included W.T.Astbury, C.H.Waddington and D.Wrinch, as well as J.F.Danielli, a surface chemist, and H.Davson, a physiologist from University College, London.

Finally, in November of the same year the previously mentioned discussion on the protein molecule was held at the Royal Society in London. Twenty scientists from at least six disciplines read papers at this meeting. They are listed in Figure 9, Speakers at

<u>Quantum Physicists</u>	<u>X-ray Crystallographers</u>	<u>Cytologists</u>
P. Auger	W. T. Astbury	H. Bauer
K. Zimmer	J. D. Bernal	C. D. Darlington
<u>Geneticists</u>	<u>Embryologists</u>	<u>Not Known</u>
B. Ephrussi	C. H. Waddington	A. Fischer
N. W. Timofeeff- Ressovsky		L. Rapkine H. Stubbe

Figure 8

Members of the Klampenborg Conference, 1938

(Names taken from Waddington :1969, and classification according to Waddington, or known training and interests)

<u>Physical Chemists</u>	<u>X-ray Crystallographers</u>	<u>Protein Chemists</u>
T.Svedberg	K.H.Meyer	K.Linderström-
G.S.Adair	W.T.Astbury	Lang
K.O.Pedersen	G.Boehm	A.Neuberger
F.J.Philpot	D.Crowfoot	S.J.Przlecki
J.St.L.Philpot	J.D.Bernal	H.H.Weber
P.A.Small		
E.Gorter		
J.F.Danielli		
<u>Immunologists</u>	<u>Mathematicians</u>	
J.Marrack	D.Wrinch	
E.Holiday		

Figure 9

Speakers at the Royal Society Conference, 1938

(Names taken from Svedberg :1939, and classification according to nature of paper contributed, or known training and interests)

the Royal Society Conference, 1938.

In the late twenties and thirties a small informal group called the "Theoretical Biology Club" held occasional meetings. Joseph Needham, an embryologist in the biochemistry laboratory at Cambridge who was a member of the club, dedicated his book Order and Life to the other members (Needham :1936). He put their names in initial form, but these can be identified as his wife, Dorothy Needham (a biochemist), J.D.Bernal (the crystallographer), Dorothy Wrinch (mathematician and protein theorist), Max Black (a philosopher), C.H.Waddington (an embryologist), J.H.Woodger (a philosopher), J.H.Woodger's wife Eden Woodger, and B.P.Weisner (a zoologist).

Thus at least two of the protein crystallographers, Astbury and Bernal, were active in the "protein community". In addition, there is evidence to suggest that Hodgkin was also in direct contact with scientists from other backgrounds. She attended the Royal Society Discussion, and her close friendship with Wrinch has already been mentioned. When she was at Cambridge as a postgraduate, she attended the lectures of both F.G.Hopkins and Joseph Needham, and she has noted that "my closest friends were in the biochemistry laboratory" (Hodgkin :1970a). She was also very friendly with N.W.Pirie. When she was asked about meetings of the Theoretical Biology Club she replied:

I did go to one or two meetings with Waddington, to Edinburgh, but I didn't belong to it. Although we all talked about it a good deal, I don't think that it had any effect on my work. Certainly it had no direct effect. One knew about the things that were interesting, but I suppose that I knew a good deal about it. I remember looking down a microscope with Waddington, and seeing some giant chromosomes. One knew quite a lot about the ideas that were floating around in theoretical biology at the time. (Hodgkin:1970a:13)

Fankuchen was also directly involved in the protein community.

He collaborated with Bawden, Pirie and Bernal (Bawden, Pirie, Bernal and Fankuchen :1936) in a paper that has already been discussed. He wrote a joint paper with Bernal in 1941 (Bernal and Fankuchen :1941a; 1941b; 1941c) in which the authors gave a complete review of the work on viruses, and cited, among others, Bawden, Pirie, Eriksson-Quensel (physical chemist), Svedberg (physical chemist), Langmuir (physicist and protein theorist), Neurath (protein chemist), Stanley (protein chemist) and Wyckoff (an American X-ray crystallographer). Although there is no way of knowing which parts of this paper were written by Fankuchen and which parts by Bernal, it is unlikely that either was unfamiliar with any important part of the work cited. Fankuchen also joined in the cyclol controversy, although his contribution was largely crystallographic.

8.22 Other Cross-Disciplinary Contacts: the Crystal Network

The protein crystallographers maintained another type of cross-disciplinary communication -- a network which passed on crystals and samples of proteins. This sort of contact is very important to the crystallographer, and it is clear that the main workers in protein crystallography -- especially Bernal, Astbury and Hodgkin -- had many contacts of this sort, although in many cases they overlapped with the "protein community". Hodgkin noted that protein crystallography:

was largely a question of the availability of the crystals.
Of course quite a lot of crystals came into the lab.
-- people would send them in from all over the world.
(Hodgkin:1970a:4)

Linderström-Lang of Copenhagen sent Bernal crystals of lactoglobulin, and the original wet pepsin crystals came from Philpot in Sweden. Hodgkin was friendly with her old Professor of Chemistry, Robinson,

and he gave her the first insulin crystals. She was also in contact with Harington and Kekwick, two protein chemists at University College Hospital.¹ Even Perutz, who was very junior in the pre-war period and little concerned with the protein community, obtained his first crystals from Adair of the Cambridge Department of Physiology. In addition he had the use of bench space at the Molteno Institute because of the interest and support of its Director, Keilin. Astbury developed his own set of contacts, although in certain respects his needs were rather different (keratin being always available in the form of wool and hair). One of his most important sources of material was Schmidt of Geissen, who supplied him with elastoidin and sodium thymonucleate.

8.23 Summary

It is not necessary to give a full list of these sorts of contacts, as it is clear that they existed for all protein crystallographers. The main purpose of this section is to demonstrate the existence of the protein community. It has been suggested that Bernal, Astbury and Hodgkin were active members, as was probably Fankuchen. Riley and Perutz were probably less involved, perhaps because they were much more junior.

8.3 Attitudes to Protein X-ray Crystallography in the late Thirties

8.31 The Direct Approach: Perutz

Perutz adopted and developed a direct crystallographic assault on protein structure, hoping in this way to improve methods to the

1. This account is based on Hodgkin and Riley :1968, and Hodgkin :1970a.

point where such work would be successful. If the titles of his papers are examined, it can be seen that his approach was almost always a crystallographic one. His first paper was written jointly with Bernal and Fankuchen (Bernal, Fankuchen and Perutz :1938). This was a straightforward account of haemoglobin, giving the unit cell dimensions and the molecular weight. The second (Perutz :1939a) was on haemoglobin absorption spectra. Through this work (which was crystallographic, but did not use X-rays) Perutz established a preliminary orientation for the haem groups. The third paper (:1942b) was a similar calculation for oxyhaemoglobin. Perutz spent much of the war studying the nature of the swelling and shrinking process. The relationship between different crystal volumes was studied in detail for horse methaemoglobin (:1946a) and for sheep methaemoglobin (Kendrew and Perutz :1948a). In a paper published in 1947 (Boyes-Watson, Davidson and Perutz :1947) he established by crystallographic means that expansion and contraction were due to water between the haemoglobin molecules rather than changing molecular shape. The "hat box" theory of haemoglobin molecular packing was advanced in this paper. The molecules were seen to be sheets of hat boxes, separated by water. Two dimensional Patterson projections suggested that bundles of protein chains were arranged parallel to the a axis of the crystal. In 1949 (Perutz :1949b) a three dimensional Patterson projection was calculated, and from this it was deduced that the interior of the molecule contained rod-like areas of high electron density.

Patterson projections played a very important part in this work. Bragg has written:

For a long time the idea that the molecule contained . .

some kind of regular structure of protein chains, which would give a strongly defined character to a Patterson synthesis was a guiding star which encouraged the investigations. As events turned out, it was a false star. (Bragg W.L. :1965c:4)

In 1950, Perutz, Kendrew and Bragg (Bragg W.L., Kendrew and Perutz :1950) attempted to build a model of the α -helix. This attempt, which was not successful, cannot strictly be described as a purely crystallographic contribution, although much of the data used was crystallographic in origin.

Perutz' later papers will not be discussed here, as they are described in Chapter 9. They are virtually all X-ray crystallographic studies of haemoglobin, and there are only a couple of partial exceptions. One was on solubility studies of the haemoglobin of sickle cell anaemia, written jointly with two non-crystallographers, Liquori of the Molteno Institute, and Erich of the Brooklyn Polymer Institute. The other was written jointly with Ingram and Gibson of the University of Southampton, in which the orientation of haem groups in haemoglobin was measured by means of electron spin resonance. (Ingram, Gibson and Perutz :1956). The impetus for this paper came, however, entirely from Ingram (Kendrew :1970a:7), and Kendrew and Perutz acted as advisors, looking upon the work as a useful source of data.

Between 1939 and 1969 Perutz published at least fifteen papers on X-ray crystallographic approaches to the structure of haemoglobin. The few papers that were not crystallographic do not undermine the proposition that Perutz was first and foremost a crystallographer.¹ Furthermore, Perutz' approach was a frontal

1. He also wrote a few papers on glaciology, his main hobby, but these had no connection with his professional interests.

one, first by means of Patterson and swelling and shrinking methods, and then after 1954 by means of heavy atom replacements. His contacts with non-crystallographers did not lead him to do extensive non-crystallographic work. His papers used largely crystallographic data, and for the most part discussed only haemoglobin. Sometimes non-crystallographic contacts were important. Through the work on sickle-cell anaemia mentioned above he learned about the heavy atom attachments in haemoglobin. He has noted:

I was sent a set of reprints from A. Riggs who was working at Harvard, who had made a mercury compound of haemoglobin and showed that it was still physiologically active. I jumped at this immediately These papers had been in the Journal of General Physiology which I would not normally have read. They were sent because I had been working on sickle-cell anaemia which Riggs was interested in. (Perutz :1970c:4)

He has also noted that:

This work on sickle-cell anaemia occupied all my time for a period, although it was a sideline; it sustained my morale during a difficult period. (Perutz :1970c:4)

He also maintained contacts with biochemists, having attended every International Congress of Biochemistry since 1949 (Perutz :1970c:6). His contacts with Sanger also started before the Laboratory of Molecular Biology was set up (Perutz :1970c:6).

He did not believe that solving the structures of proteins would be easy, and at the beginning he did not formulate it as a possibility.

He has noted that:

Little was known about proteins, their shape was not known. Others were doing work on their sedimentation rates, and their viscosity, and the question arose as to whether X-ray analysis might be any use. Certainly, at the beginning, I did not think of solving the complete structure. (Perutz :1970b:2)

His persistence in this work is all the more remarkable in view of the fact that many crystallographers and others looked upon the whole enterprise with considerable scepticism. Kendrew, speaking

of his arrival at Cambridge after the war said:

Max ... (had) been on this thing for a very long time, he started before the war, and really, its incredible actually, how persistent that man's been in following this thing through, very much further than the rest

Interviewer Fighting ... what was he fighting against? Were people not expecting him to do it?

Kendrew Well, you see, I think people outside, as it were, thought it all a bit of a mad business altogether ... They thought it probably couldn't be done; it seemed a very complicated problem and by ordinary standards anyone tackling it might have seemed a bit crazy.

Interviewer And did this continue after you'd joined Perutz?

Kendrew Oh, I think a lot of people -- they might not admit it now -- I think for quite a number of years after we got going together, this would still have been the opinion among biologists and crystallographers.

Interviewer Dr. Kendrew, how do you react in person to being thought a bit mad about what you were doing? What is your reaction to that?

Kendrew Well, I don't think I cared very much ... You know looking back on it I sometimes think I was a bit mad myself and if I ... wonder why I ever did tackle this thing, I think it was probably ignorance, because, you see, the technique we were using was crystallography. I wasn't a crystallographer. I never learned anything about the technique I was going to use and I think perhaps this was a good thing; ... if I'd known too much about it, I might have thought it was impossible. I think it was really a case of ignorance being bliss.

(Kendrew :1962a:21)

Although Keilin was always very encouraging, many others including crystallographers were still sceptical after the first heavy atom replacements had been prepared, and the problem was solved in principle.¹ Before 1954 the crystallographers had good reason to be sceptical, in view of the technical difficulties outlined in Chapter Seven. Kendrew noted that:

... not being a professional crystallographer myself, it seemed on the face of it to be the most promising technique. And I think in this sort of situation, ignorance is good. Because if you know too much about the technique, all you know about is the difficulties. And you're put off and don't try to solve the difficult problems. And it is rather significant that nearly all the first protein crystallographers, who were

1. There were still some difficulties to overcome (Perutz :1962b:209).

successful in the field, had not been trained as crystallographers. They were outsiders who had come in rather rashly using this technique. (Kendrew :1969a:2)

Perutz, Kendrew and Hodgkin all trained originally as chemists.

In this section it has been suggested that Perutz adopted a frontal attack on the structure of haemoglobin by crystallographic means. Although he had wide contacts, particularly with biochemists, these did not reduce his commitment to crystallography. In addition, his work was the object of a certain amount of scepticism as many crystallographers and biologists found it difficult to believe that the project was viable.

8.32 The Direct Approach: Hodgkin

Although Hodgkin advocated an exclusively crystallographic approach to the complete protein molecule, she considered it advisable to develop skills and techniques by applying them to a range of molecules of gradually increasing complexity:

Interviewer Did doing protein X-ray crystallography at this stage seem practicable?

Hodgkin I don't know. It was more a question of following our noses rather than anything else. Everyone thought it would be quite nice, but it was largely a question of the availability of the crystals ... But our interest in the proteins certainly didn't mean that we weren't interested in doing other things. We could see that we weren't going to be able to do these things immediately. We could see that the order of magnitude of difficulty of these crystals was much higher, and this was a result of the size of the molecular weights and the unit cells. Of course, we had rather little experience of them at the time. But none the less, we were always looking for possible ways of going further, and we had this idea of going further right from the start. So the problems that we saw were actually those of getting heavy atoms which would be heavy enough to affect the phase angles significantly. My own idea about how to make progress was to do simpler things first, but I have never at any time completely stopped work on insulin. I held it by me while trying out methods of structural analysis on simpler molecules -- the sterols, penicillin, but I suppose that I always saw the structure of insulin as a goal. In the earlier period I tended to work on it myself, and encouraged other people to work on other things. (Hodgkin :1970a:4)

The general trend becomes clear if Hodgkin's papers in Chemical Abstracts between 1935 and 1965 are classified by subject (See Figure 10), although the bulk of the successful papers on the structure of insulin have been written since 1965 and hence do not appear in this Figure. ¹

Hodgkin has nowhere talked about the expressions of scepticism for the protein work mentioned by Perutz, Kendrew and Phillips. She was, perhaps, less exposed to criticism because she did successful work on a series of simpler molecules -- work which while aiding the protein work, also slowed it up:

Interviewer Did you ever lose faith that proteins would be solved?

Hodgkin I don't think so, because the methods and apparatus were always developing, and one could see that one was working on problems that were much more complicated than those of a few years previously. In a way I was luckier than Max Perutz in that I had other interests. I wasn't just working on one problem, but I had others which I worked on -- penicillin and B 12. But this did mean that I wasn't quite as concentrated as I might have been on protein. It took years of hard work before one came out with the final solution. In fact, those who did not concentrate at crucial times clearly did not get so far. (Hodgkin :1970a:10)

Her main interest was in the advance of heavy atom methods, which she thought could best be developed on simpler molecules (Hodgkin :1970a:10). Unlike Perutz, she was never diverted onto the swelling and shrinking method, as it was clear from the beginning that insulin was a system on which it would not work. She was a rather sceptical member of the protein community:

Interviewer Did you expect to be able to get help from non-crystallographers, for example from biochemists or physical chemists?

Hodgkin No! I don't mean to sound arrogant, but frankly, the answer is no! I think that we thought that this was a purely crystallographic problem, and that it would have to be solved by crystallographers alone. I remember going to a meeting in Leeds where a lot of people working on peptide and protein problems were getting together and all of them were

1. Insulin was successfully determined in 1969 by Hodgkin's team (Adams et al :1969).

	<u>1935-1944</u>	<u>1945-1954</u>	<u>1955-1965</u>
Sterols and Hormones	5	1	2
Proteins	8	3	1
Penicillin		3	1
Chloresteryl Iodide		1	
Vitamin B 12		2	11
Others	16	5	9

Figure 10
Hodgkin's Papers between 1935 and 1965 by Subject
and Date.

giving their own, different, evidence. I remember walking up and down with Eddie Hughes saying "There's only one way to solve this problem, and that is by X-ray crystallography." Of course, we knew what everyone was doing, but we really did feel that nothing except X-ray analysis would give us what we wanted. The kind of information that we wanted was the organisation of the molecules, and X-ray crystallography was the only way that we were going to get it.

Of course, it would have been absurd to refuse to consider work on something like the chemical sequencing of insulin. There was no pulling apart there. We were waiting hands out for the sequence when it was determined. No, it was obviously useful to have all these things, but I think that the only thing that could be done that would get us our answer was X-ray analysis. The other things were useful and necessary, but the most important things were (1) isolation and purification, (2) the chemical sequencing, and (3) the X-ray analysis. It was only after all this was done that other data, such as that gained by infra-red spectroscopy and NMR became interpretable.

(Hodgkin :1970a:9)

In this section the attitude to protein crystallography expounded by Hodgkin has been outlined and illustrated. This was a purely crystallographic approach, owing little to advances in chemistry. Hodgkin developed techniques, and in particular the heavy atom replacement technique, by applying it to molecules that were simpler than the proteins.

8.33 The Direct Approach: Bernal

Bernal believed that a direct crystallographic approach to the proteins was possible, but that it was necessary to develop certain methods (in particular computing and photography) if success was to be achieved.

This attitude was mixed with another -- that it was necessary to utilise all possible sources of information, no matter what their disciplinary origin, in order to elucidate the structure of the proteins. The fact that Bernal was, in the first place a crystallographer, can be seen by his commitment to crystallographic work in a wide range of areas away from the proteins. These assertions will

now be supported.

In 1939 Bernal (:1939c:663) surveyed progress in the field of protein studies, and mentioned three new methods that had been responsible for many recent advances: the centrifuge; X-ray crystallography; and "electrical" methods. X-ray crystallography was limited in its power by the phase problem, and Bernal suggested that the only way round it was through:

the introduction of a heavy atom, or the observation of intensity changes on dehydration ... (Bernal :1939c:665)

He felt that the X-ray method had been chiefly valuable up to that time for its ability to disprove hypothetical protein structures put forward. He concluded by noting that:

The picture thus presented is far from being a finished or even a satisfactory one. The crucial fact that requires elucidation is the precise mode of folding or coiling of the peptide chains, and for this we may have to wait for some considerable time, until the technique of X-ray and other methods have been advanced much further than at present. The problem of the protein structure is now a definite and not unattainable goal, but for success it requires a degree of collaboration between research workers which has not yet been reached. Most of the work on proteins at present is uncoordinated; different workers examine different proteins by different techniques, whereas a concentrated and planned attack would probably save much effort which is now wasted, and lead to an immediate clarifying of the problem.

(Bernal :1939c:667)

Thus at this time Bernal was actively advocating cross-disciplinary studies of proteins. Snow has described Bernal's position rather more graphically:

This was the start of molecular biology. He not only used his own techniques, he acted as an impresario for bringing in other scientists with other physical weapons, or as the middle-man -- if one wants to personify the situation -- between the Cavendish of Rutherford and the biochemical laboratory of Hopkins. The other form of Cambridge thought was Gowland Hopkins, the father of Biochemistry. (Snow :1966:26)

Yet Bernal's own writing on the relationship between chemistry and X-ray crystallography was not always consistent, for despite the

the emphasis that he placed on collaboration, he also attached unique importance to the X-ray method:

By the time the second world war came, the next stage of the problem of crystalline protein structure was fairly clear. What was not clear yet was along which line of research would the solution first be found. The chemical method had not yet yielded, but was clearly bound to yield, the primary structure of a protein polypeptide. The X-ray study of the globular proteins in a crystalline form showed an enormously rich mine of information but it was, apart from molecular size, uninterpretable; either a hypothesis of a structure had to be made or a new method of finding the phases of the X-ray diffraction had to be developed.

The former approach was the first to be tried and led to a long and ultimately fruitless search for a structure, ... I had then said that if the structure of protein were simple we should soon find it out. In fact, it was not, and took about twenty to twenty-five years to work out. ... Meanwhile, a much slower, surer but more roundabout approach was being developed by Pauling and his crystallographic collaborator, Corey.

(Bernal :1963a:23)

The above was written with hindsight in 1962. What follows has been written even more recently:

By 1940 it was clear that a successful attack on the complete protein structure could be made, but there were still many difficulties. Two modes of attack suggested themselves: the first was a straightforward X-ray crystallographic study of crystalline protein, using all the techniques of an advanced crystal analysis. Computers were not available for this until much later, in the mid 1950's. The second was a model building method based on exact knowledge of the structure of the amino acids and smaller peptides themselves and an attempt to build up the protein a priori and then check the structure by X-ray methods. I remember very well discussing the problem with Pauling just before the war. He was in favor of the second method, which I thought indirect and liable to take a very long time. Nevertheless, it was Pauling's ideas that were to have a decisive effect on the result. (Bernal :1968a:372)

Thus, Bernal thought that a direct approach to protein structures by crystallographic methods, allied to other chemical and physical methods, was the best way of ensuring success. The optimism about a direct crystallographic approach was probably informed by a belief, or at least a hope, that protein structure would turn out to be relatively regular (Bernal :1963a:23). This belief was

consistent with the various simple theories of protein structure that were current in the late thirties. If Bernal's attitude to collaboration was complex, his ideas about the direction of protein crystallography were clear. This attitude, which was discussed in Chapter Four, was summarised after the war in his own words:

The attack on the central problem of protein structure is being carried out at the very limit of existing techniques and to make effective progress it will be necessary at the same time to improve both the experimental and theoretical tools available to the X-ray worker. For this purpose an electronics section and an electronic computer section have been added to the laboratory. (Bernal :1948a:4)

Despite his interest in collaboration, Bernal was not the less concerned with the development of methods in crystallography. He wished to see these developed to a point where it was possible to determine the structure of a protein. He was always first and foremost a crystallographer, and his commitment to crystallography can be illustrated by two final quotations. The first concerns the wide range of subjects that Bernal studied by X-ray crystallography in the post war years:

He had ... extremely practical ideas about the kind of research a country recovering from war should undertake. He became interested in problems of cement and concrete formation, encouraged by the Building Research Station, in coal oxidation with the support of the Coal Board, in the structure and properties of gluten for the Flour Miller's Association and in the structure of pulverised fuel ash for the Central Electricity Authority. (Hodgkin :1969a:9)

The second concerns the development of molecular biology. Although he has, in other places, traced its roots to several different disciplines (Bernal :1963a:21) he has also written:

My own interest in genetics was not political or philosophical, but a logical consequence of the development of molecular biology, which I considered to be a branch of generalised crystallography.

(Bernal :1968b; quoted with the permission of P.G.Werskey)

8.34 Indirect Approach: Pauling

Pauling considered that the best way to make progress in determining the structure of proteins was to carry out crystallographic studies of component parts -- for example of amino-acids and short lengths of polypeptide chain. He felt that the direct approach, exemplified by the work of Bernal, Perutz and Hodgkin, was unlikely to lead to success.

Pauling's attitude (which was mentioned in the above section on Bernal (:1968a:372; 1963a:23)) rested on the following factors:

(a) A belief that the crystallographic methods available neither actually nor potentially offered a means for direct protein structure determination.

(b) A background in structural chemistry that gave him extensive knowledge of permissible bond angles and lengths. The classic paper in this area was The Nature of the Chemical Bond which was published in 1931 (Pauling :1931). As a result of this background Pauling was always very critical of ill-founded attempts at model-building. Thus Bernal wrote:

Pauling was shocked by the freedom with which the X-ray crystallographers of the time, including particularly Astbury, played with the intimate chemical structure of their models. They seemed to think that if the atoms were arranged in the right order and about the right distance apart, that was all that mattered, that no further restrictions need be put on them.
(Bernal :1963a:23)

Pauling and Niemann developed a scathing attack on the cyclol theory, which in their view violated both X-ray crystallographic and energy criteria:

Since denatured proteins are known to consist of polypeptide chains, and native proteins differ in energy from denatured proteins by only a very small amount (less than 1 kcal. / mole per residue), we draw the rigorous conclusion that the cyclol structure cannot be of primary importance for proteins;

if it occurs at all (which is unlikely because of its great energetic disadvantage relative to polypeptide chains) not more than about three per cent. of the amino acid residues could possess this configuration.

(Pauling and Niemann :1939:1863)

This background in structural chemistry led Pauling to a piecemeal approach. He was disposed to construct models of proteins rather than attempt a direct analysis, but the models were to be accurate, and not sloppy like many model-building attempts. The amino-acid structures were determined with great accuracy at Pauling's laboratory by Corey the crystallographer, who was a close collaborator.

Pauling's approach was fruitful in that it led to the solution of the structure of the α -helix (Pauling, Corey and Branson :1951).

Here the authors wrote:

During the past fifteen years we have been attacking the problem of the structure of proteins in several ways. One of these ways is the complete and accurate determination of the crystal structure of amino acids, peptides, and other simple substances related to proteins, in order that information about interatomic distances, bond angles, and other configurational parameters might be obtained that would permit the reliable prediction of reasonable configurations for the polypeptide chain. We have now used this information to construct two reasonable hydrogen-bonded helical configurations for the polypeptide chain; we think that it is likely that these configurations constitute an important part of the structure of both fibrous and globular proteins, as well as of synthetic polypeptides.

(Pauling, Corey and Branson :1951:205)

Bernal wrote of this work:

... Pauling made the same simplifying and incorrect assumption that the structure of the globular proteins consisted of rods of polypeptides arranged parallel to each other in different kinds of order. Crick was able to show that this was incompatible with the intensities of the X-ray reflections, which ought to be, on this hypothesis, much stronger than those observed. I had said that if the structure of globular proteins was simple, we should be able to find it out relatively quickly, but, in fact, it took years and the structure was not a simple one. It now appears that the only thing that was wrong in Pauling's hypothesis, but carefully not stated, was the implication that the α -helix was an important structural

feature of all globular proteins. If it had been stated as some globular proteins, it would have been correct as well as illuminating. (Bernal :1968a:375)

In the end, important though the structure of the α -helix was, it was by direct crystallographic methods of the sort originally envisaged by Bernal, Perutz and Hodgkin, that the structure of the globular proteins was elucidated.

No further account of Pauling's attitude or work will be given here, as he is neither British, nor strictly speaking a protein crystallographer. It can be seen, none the less, that his attitude was in contrast to that of Bernal, and how they both, in their different ways, gained a measure of success.

8.35 The Combined Approach: Astbury

Astbury, unlike Bernal, Hodgkin and Perutz developed his interests to a point where he was no longer, first and foremost, a crystallographer. He did not abandon X-ray crystallography -- he used it as an important technique in its own right -- but by 1945 he looked upon himself primarily as a molecular biologist, and wished to employ all relevant means for the elucidation of molecular structure.

In the 1951 Harvey Lecture he said:

The name "molecular biology" seems to be passing now into fairly common use, and I am glad of that because, though it is unlikely I invented it first, I am fond of it and have long tried to propagate it. It implies not so much a technique as an approach, an approach from the viewpoint of the so-called basic sciences with the leading idea of searching below the large-scale manifestations of classical biology for the corresponding molecular plan. It is concerned primarily with the forms of biological molecules, and with the evolution, exploitation and ramification of those forms in the ascent to higher and higher levels of organization. Molecular biology is predominantly three-dimensional and structural -- which does not mean, however, that it is merely a refinement of morphology. It must of necessity enquire at the same time into genesis and function.

I think it might be worthwhile explaining how I myself, classified primarily as a physicist, came to find myself in this galley -- how I "discovered" molecular biology, if you like.

(Astbury :1951:3)

In 1961, in correspondence to Nature he came back to the topic. Having quoted the above and discussed various morphological studies being carried out at his laboratory, he added:

I trust that Prof. Waddington will not mind my recalling in this way our original concept of molecular biology, and will agree that we have kept fairly faithfully to it. It is impossible, though, to embark seriously on work of this kind without being interested in, and becoming more and more involved in, numerous associated studies, with the result that, as has happened, there soon comes a time when there seems no end to the business. Molecular biology has now inevitably spread to all aspects of biology looked at from fundamental molecular viewpoints -- and this includes 'molecular genetics', for example, if I may dare suggest it; and it is difficult to maintain that such an eventual extrapolation is unwarranted, for it is simply saying that it is the coming biology. (Astbury :1961a:1124)

It seems that in the post war years Astbury looked upon himself as a molecular biologist.

Although he gave no precise description of the techniques that he would expect a molecular biologist (in the narrower 1951 sense) to use, he did mention a number of techniques in a discussion of work on rheumatoid subcutaneous nodules. The idea, he noted, was to explore sections of the nodules point by point:

and for each point to correlate the findings of four methods: (a) classical histology; (b) X-ray diffraction analysis; (c) electron microscopy; and (d) micro-biochemistry; the whole in relation to clinical observations besides. (Astbury :1951:35)

In 1945 Astbury was made Professor of Biomolecular Structure.

Ewald wrote of this, that his work on wool:

makes it necessary to combine with it all possible evidence that can be gleaned from (its) physical and chemical behaviour -- a discussion that often requires great imagination. It was hereby that Astbury's unsinkable optimism helped him along where more anxious scientists might have feared to tread. The designation of the Department for Astbury was the first of its kind, and Astbury was proud of the name: Biomolecular Structure; this type of name has since been adopted by departments or laboratories in other universities, British and foreign. As Astbury conceived it, it was to be a place where biological structure and texture on the molecular scale could be attacked in a catch-as-catch-can style, using

chemical, physical, and biological properties in conjunction with microscopy, electron microscopy, X-ray and electron diffraction and whatever else appeared hopeful.

(Ewald :1962:354)

Astbury himself gave an account of the naming of the Department:

... when in 1945 I was appointed professor, the university committee considering me, and from which I was naturally excluded, preferred the name 'biomolecular structure' to 'molecular biology', which was what I myself wanted. Presumably, a majority of the members of that committee held opinions similar to those expressed by Prof. Waddington, and I offer this argument in his support; though I will confess that a probably more candid, and conceivably better justified, assessment that leaked out to me was that "he may know something about molecules but he knows precious little about biology".

(Astbury :1961a:1124)

The manner in which Astbury became more general, more "molecular biological" in his interests can be gauged from Figure 11. He wrote no biological papers before 1928 and only two non-biological papers thereafter. While X-ray crystallography was the most important technique in his early work, electron microscopy also became important after 1940. He wrote a large number of papers, from 1929 onwards, on the theory of protein structure, and although these depended in part on crystallographic data, their contribution was normally at a more general level, with data drawn from a number of different sources in the protein community.

It was mentioned in Chapter Four that on several occasions Astbury outlined the special difficulties facing the fibre X-ray crystallographers. Thus in 1935 (Astbury and Sisson :1935 :533) he suggested that best progress must depend on the interpretation of X-ray photographs in relation to other physical and chemical data. The same point of view was expressed in 1940 (Astbury and Dickinson :1940:324) and it is clear from other quotations (Astbury and Dickinson :1936:909) that he sought collaboration with chemists and others in the protein community.

	<u>- 1928</u>	<u>1929 - 39</u>	<u>1940 - 50</u>	<u>1951 - 61</u>
<u>X-ray Crystallography</u>				
Methods	3	1	1	
Non-biological structures	4			
Keratin		16	4	7
Other Proteins		10	7	3
Artificial Fibres			8	
Nucleic Acid		1	1	
Plants and Plant Cells		3	3	2
Bacteria			1	4
<u>Protein Theory</u>		11	8	5
<u>Electron Microscopy</u>			6	3
<u>Other</u>		3	11	11

Figure 11

Astbury's papers by Date, Subject, and Method

(Taken from the bibliography in Bernal :1963a; papers classified according to title. A few have been counted twice)

Astbury was concerned with a subject matter that rendered impossible, sure advance along purely crystallographic lines. In the case of globular proteins, detail was clearly present down to the 2.0A. level. The fibre photographs were always messy and imprecise, however. As a result of this, Astbury leaned heavily on other methods and members of the protein community. This can be seen from his postwar commitment to "biomolecular structure" and molecular biology, in which all manner of useful approaches were drawn in. There was no strong commitment to crystallography alone.

8.36 Other Crystallographic Attitudes

Some crystallographers thought that the technical problems involved in protein work were so great that it was better to stick to simpler molecules. This attitude, which was certainly very prevalent in the forties and fifties, may have been less widespread in the thirties. Other crystallographers offered encouragement and support to the protein workers at times. Thus Robertson, an organic X-ray crystallographer who never himself did any work on the proteins, suggested that the heavy atom method might offer a way of determining the structure of insulin. He noted:

It may be going too far to suggest that the insulin structure could be determined in this way. The molecule does, however, contain a few zinc atoms, and if these could be replaced with mercury, as has been suggested, a very profitable study might ensue. (Robertson :1939:76)

More recently Robertson has noted that he often toyed with the idea of working on proteins, but:

there were too many other exciting things to do, more within the area of organic chemistry. These were things that I knew that I could do. The protein work, you see, was very long term. Max Perutz has spent a whole lifetime doing haemoglobin. And another thing that put me off was the fact that you really have to be, or at least have access to biochemists, especially so that the isomorphous replacement derivatives can be made.

To make them you really have to be a trained biochemist.
(Robertson :1970:2)

Thus, although he did no work on proteins himself, Robertson cannot be described as one of what Phillips called the "scoffers" (Phillips :1970:10).

The available data does not indicate whether Robertson's attitude was widespread. However, the contrary attitude, one of scepticism, was very common in the post war period. Beevers, an organic crystallographer, recently noted that he thought the protein work was "impossible" (Beevers :1970:6), but such expressions of scepticism are not easily discovered now that the protein work has been so successful. Phillips noted, however, that:

Many of the professional crystallographers were extremely sceptical about the whole business. They regarded it as a complete waste of time. If any of the protein crystallographers made a mistake, then there was much jeering. I was aware of this feeling, because Howells, the other PhD student at Cardiff had gone to join Perutz. In the U.S. I found that there was more scepticism -- and I got to know Harker at Brooklyn and his work on ribonuclease, and I found that he was also being jeered at. So, I suppose that I began to regard protein as a sort of challenge, so when Bragg's letter arrived I took the offer up. (Phillips :1970:5)

Mrs. Ehrenberg, who worked with C.H. Carlisle, put it like this in a recent interview:

Interviewer I have had the impression that conventional X-ray crystallographers were sceptical about the protein workers.
Mrs. Ehrenberg Yes, this is true, and you can understand why. If you take a simple organic molecule, you have perhaps 800 or 1000 reflections to measure. In proteins you have ten, twenty, or thirty thousand to measure, and to which you have to assign an index. That is even before you use the information. ... Look at Dorothy Hodgkin. For thirty years she was virtually a slave to insulin, and it was really horrible to do. There were so many possibilities. (Ehrenberg :1970:8)

Further descriptions of the scepticism by Perutz (:1962b:209) and Kendrew (:1969a:2; 1962a:21) have already been quoted or mentioned. Even W.L. Bragg, who was strongly in favour of Perutz' and Kendrew's

work, thought of it as having a "chance of success indistinguishable from zero" in 1947 (Bragg W.L.:1963a:4). Fankuchen, who was central to pre war work on protein structure, became sceptical after the war (although when myoglobin was successfully structured in 1958 he was the first to admit that his scepticism had been misplaced (Kendrew :1970a:3)).

The scepticism did not seriously affect the extent of professional communication between the protein workers and other crystallographers. Hodgkin notes:

We always talked to other crystallographers. There was never a time when nothing was happening. At every meeting there would be papers on protein analysis. (Hodgkin :1970a:9)

Phillips noted:

I went on going to scientific meetings. I went to the IUCr international meeting at Paris in 1954, but I didn't go to the one in Montreal in 1957 -- I suppose that might be a sign of being a little more cut off. By the 1960 meeting at Cambridge we had results, and the scoffers were silenced. And certainly I went on going to XRAG meetings at London -- and there was certainly general exchange of techniques and views. I don't think that we were really cut off. (Phillips :1970:10).

8.37 Attitudes of Non-Crystallographers

Some non-crystallographers attached great importance to the work of the protein crystallographers. In 1936 Needham, the embryologist, wrote:

Of the new means of heightening our acuity of vision, the most powerful is without doubt the use of X-radiation.
(Needham :1936:142)

Again:

But for the present argument one of the most important results of Astbury and his colleagues (in whose writings lies so much of value for the future of biology) was their establishment of the chain-like nature of the protein molecules in such crystals. (Needham :1936:144)

And yet again:

The importance of this work on the crystal structure of animal fibres can hardly be overestimated. Is not biology as

a whole very largely the exploration of fibre properties?
(Needham :1936:146)

Svedberg, in his opening address at the Royal Society Discussion on the protein molecule, noted:

X-ray analysis of protein crystals and semi-solid protein deposits in living organisms has yielded results of the highest importance for the elucidation of the structure of the protein molecule. Investigations by the two British schools have shown that the proteins may be divided into two classes, ...
(Svedberg :1939:46)

Finally F.C.Bawden, the virologist, wrote in 1942:

Of the many techniques introduced into research on viruses during recent years, none has aroused more interest than those of the crystallographer. The value of these techniques in such work is amply shown in three recent papers by Prof. J.D.Bernal and Dr. I.Fankuchen. The authors describe these papers as "only a preliminary and rough survey" and state that "many more years of work will be needed before exact and reliable interpretations can be expected". No doubt this is true. Nevertheless, what has already been done has greatly widened our understanding of viruses, in addition to bringing to light unsuspected properties of colloidal aggregates. (Bawden :1942a:321)

Although this is obviously not a full survey, it is clear that some members of the protein community thought that the work on proteins by the X-ray crystallographers was very important.

8.38 Summary

Eight different attitudes to developments and progress in protein X-ray crystallography in the late thirties have been outlined. They were not mutually exclusive in all cases. The attitudes of Bernal, Hodgkin and Perutz appear sharper than they probably were, and it is doubtful whether they can be thought of as having had points of view that were seriously incompatible. The translation of these attitudes into action has also been illustrated.

8.4 Conclusion

Evidence has been presented above concerning the existence of a "protein community". Different attitudes to collaboration with

non-crystallographers have been described and illustrated. It has been suggested that there were two main attitudes in the British community of protein crystallographers:

- (1) Cross-disciplinary collaboration was seen to be essential. This attitude was expressed by Astbury who became so committed to a cross-disciplinary effort that he came to look upon himself, first and foremost, as a molecular biologist.
- (2) The attitude manifested by Bernal, Hodgkin and Perutz, who felt that while chemical and other data might be useful in varying degrees, that none the less the main problem was crystallographic. Naturally they found it necessary to have access to protein chemists, or chemical facilities, in order to prepare crystals and heavy atom derivatives. These workers thought of themselves first and foremost as crystallographers.

The difference between Astbury and the others arose at least in part because of their different subject matters. The study of fibres by X-ray diffraction was clearly never going to lead to a complete structural solution, while in the case of the globular proteins it was obvious from 1934 on, that all the necessary detail existed in the X-ray picture, if only it could be interpreted. The main work of Bernal and the others consisted in trying to interpret that detail. Astbury's approach to the globular proteins was quite different. He tried to generalise from his work on the fibrous proteins and suggest ways in which the polypeptide chains folded in globular proteins.¹ The approach of Bernal, Hodgkin and Perutz was crystallographic. The approach of Astbury was synthetic and

1. See, for example, Astbury :1951.

theoretical -- he wished to build a theory with X-ray, chemical, centrifugal and other data. Indeed, Hodgkin has suggested that Astbury's approach was criticised by Perutz and Fankuchen:

Astbury was criticised by Perutz and Fankuchen mainly because the thought that he gave the impression that too much could be found out about protein from fibre proteins. (Hodgkin:1971a)

The difference between the workers is further underlined by recalling the Departments in which they worked. While Astbury worked in the Department of Textile Industries until 1945, when he; became Professor of Biomolecular Structure, Bernal worked in Physics Departments at Cambridge and London, Perutz worked in the Cavendish until 1962, and Hodgkin worked mainly in the Department of Chemical Crystallography at Oxford. The Textile Industries Department was cross-disciplinary and practically oriented, while this was not true of the others.

The commitment of Bernal, Hodgkin and Perutz to crystallographic methods in the post-war period can be seen from the work they organised and carried out. Bernal studied a wide range of practical problems by means of X-ray diffraction. In the period 1929 to 1939, he published X-ray papers on methods, inorganic structures, small biological molecules, proteins, viruses, water and the theory of crystals. In the period 1940 to 1967 he again published in all these areas. Hodgkin did important work on smaller molecules, while Perutz singlemindedly worked, again by X-ray methods, on the structure of haemoglobin.

9 THE POSTWAR WORK OF PERUTZ, KENDREW, CRICK, PHILLIPS AND HODGKIN

9.1 Introduction

After 1945 the most important work in British crystallography was carried out by Perutz, Kendrew, Crick, Hodgkin and Phillips and their collaborators. The justification for this assertion is simply that they were successful in solving the structures of four proteins -- myoglobin in 1958, haemoglobin in 1960, lysozyme in 1962 and insulin in 1969. Myoglobin and haemoglobin were the first crystalline proteins that were successfully structured, and this success put Perutz and Kendrew in the front league of crystallographers.

In this section the work of the above crystallographers will be discussed. The emphasis in this account will be on the development of techniques and methods.

9.2 Perutz: The "Hatbox" Model

The first important postwar paper in haemoglobin (Boyes Watson, Davidson and Perutz :1947) opened with a general review of the scope and state of protein theory, in which the authors mentioned the work of the biochemists Chibnall, Syngé and Sanger, and Astbury's work on polypeptide chains. They noted that:

there is need both for detailed investigations of the structure of individual crystalline proteins and for comparative studies of the structural characteristics of different types of groups of proteins. Perhaps the most powerful method of studying the molecular structure of intact proteins is single crystal X-ray analysis. The present investigation is an attempt to derive the maximum information that this method can provide from a study of the crystal structure of horse methaemoglobin.

(Boyes Watson, Davidson and Perutz :1947:84)

This problem was more complex than anything previously attempted in X-ray crystallography, and the paper was "admittedly a very limited advance". They described experiments to determine the location of the water of crystallisation, which they suggested was in layers between protein layers. The protein molecules themselves did not alter their shapes when the crystal took up or gave out water. The method used was to introduce ions with heavy atoms into the water of crystallisation, and to examine the consequent changes in intensity reflections. The molecules of haemoglobin appeared:

to be a cylindrical disk of an average height of 34 Å with a slightly convex circular base of 57 Å diameter. This (illustration) is merely a simplified, diagrammatic picture, giving as it were the fuzzy outline of the molecule, whose surface could not possibly be as smooth as this drawing suggests.

(Boyce Watson, Davidson and Perutz :1947:122)

This was the beginning of the "hatbox" theory of haemoglobin. The molecules were pictured as cylinders, close packed, and in sheets.

Much of this paper depended on the calculation of one-dimensional Fourier series. The phases were determined in various ways. Firstly there was what the authors called the "isomorphous exchange method" -- an attempt to calculate the phases of the amplitudes of the $00\bar{1}$ reflections by calculating the phase contributions of the heavy ions in the liquid. There were problems in this approach which resulted in a choice between two alternative results. Fortunately, one of these was obviously untenable, so it proved possible to determine the signs of some of the $00\bar{1}$ reflections.

Secondly there was the "nodal point method" in which an attempt was made to trace the curve of the molecular structure amplitude on a line normal to the layer plane. As there was no direct way of

doing this, the points where the appropriate reflections reached zero intensity and started to rise again at different stages of swelling and shrinking were determined. It was not possible to deduce the absolute signs from this although in some cases the relationship between the signs of different reflections was discovered.

The third method, the "layer structure method" was an attempt to determine the signs by trial and error. Patterson projections suggested that the protein layers each contained secondary scattering layers parallel to the layer plane which determined the signs of the 001 reflections. Calculations were made for from two to five layers, and it was found that only the model with four layers gave a sign for the 002 reflection which was similar to that actually found in experiment.

Thus the three methods corroborated each other to some extent, and it proved possible to calculate a one-dimensional Fourier series which gave the electron density in this dimension. Knowing this, and the fact that the most important distances between scattering matter in the molecule were from 9 to 11 Å apart, the authors noted:

We have refrained, so far, from offering any detailed interpretation of the one-dimensional Fourier synthesis or of the Patterson projections. Such interpretation is comparatively easy in the light of current ideas of polypeptide chain structure; the present difficulty is that almost any model based on a folded polypeptide chain structure agrees with the main features of the X-ray data. In view of the four prominent peaks on the one-dimensional Fourier projections it is tempting to propose a four-layered structure with the backbones of the polypeptide chains in the plane of the layers and the side chains protruding above and below, but the X-ray data do not prove its correctness, they are merely compatible with it.

(Boyes Watson, Davidson and Perutz :1947:125)

In the second paper in the series (Perutz :1949b) a three dimensional Patterson synthesis was calculated. Perutz wrote:

The actual chances of interpretation depend largely on the kind of molecular structure which the protein may be supposed to possess. For instance, if the globin molecule consisted of a complex interlocking system of coiled polypeptide chains where interatomic vectors occur with equal frequency in all possible directions, the Patterson synthesis would be unlikely to provide a clue to the structure. On the other hand, if the polypeptide chains were arranged in layers or parallel bundles, interatomic vectors within the layer plane or in the chain direction should appear particularly frequently and should give rise to a vector structure showing a corresponding system of layers or chains, which could then be interpreted without difficulty. All the more plausible hypotheses of globular protein structure put forward in recent years have been based on systems of the latter kind. Hence it was not unreasonable to hope that the Patterson synthesis might lead to interpretable results which would justify the great effort involved in its preparation.

(Perutz :1949b:474)

Data extending down to a resolution of 2.8 Å. were used. Perutz wrote that:

the limiting sphere contained 62,700 reciprocal lattice points which symmetry reduces to 7840 reflexions relevant for analysis. The photographing, indexing, measuring, correcting and correlating of some 7,000 reflexions was a task whose length and tediousness it will be better not to describe.

(Perutz :1949b:475)

The calculation was equally tedious. Bragg (Bragg W.L.:1965c:3) suggested that it was the first in which an electronic computer was used, but in the paper itself Perutz mentioned the use of the Hollerith Card Machine. The Patterson projections revealed a shell of high vector density at a distance of 5.0 Å. from the origin and

a rod-like structure of high vector density which is centred at $z = 0$ and runs parallel to X . This rod contains four maxima along its length which are spaced at intervals of 5.0 Å.

(Perutz :1949b:485)

In addition to the above there were three more rods of high density at about 10 to 11 Å. from the X axis, and four more at about 10 Å. from the Y axis. Perutz suggested that:

the haemoglobin molecule contains chains parallel to X with a prominent vector of 5 Å along the chain direction and a distance

of 10.5Å between neighbouring chains. This conclusion emerges from the vector structure alone (Perutz :1949b:488)

There was overwhelming chemical and physical evidence that there were polypeptide chains in globular molecules. The links within the chains were probably of primary co-valent nature, while those between neighbouring chains were salt bridges, and secondary valence bonds. It seemed likely that a bundle of polypeptide chains would produce a vector map such as the one described above, and it was very unlikely that the vector rods represented any other kind of chain.

Perutz advanced a model in which there were six chains, folded backwards and forwards. This rested on chemical evidence of Porter and Sanger, and well known crystallographic packing principles. Perutz drew two diagrams showing the type of configuration and packing possible. This model was consistent with the data outlined above, but there were two main difficulties in such an interpretation. One of these was the first cause of the breakdown of the parallel chain model. Perutz asked:

Would it not be more satisfactory to base interpretation on a rigorous mathematical correlation between postulated molecular structure and the observed vector structure, rather than to work with qualitative arguments and imponderable probabilities?

....

... no entirely satisfying answer can at present be given. In singling out the system of rods as the basis of interpretation the writer was led mainly by the excellent correlation between the rod-like structures in the three-dimensional synthesis, and certain features of the planar projections, The agreement of the distances both within and between the polypeptide chains in haemoglobin with those found in fibrous proteins (...) convinced him that these were significant features which provide the clue to the structure

... Any mathematical correlation between a postulated molecular structure and the observed vector structure really amounts to a comparison of calculated and observed intensities, which will remain impossible as long as the details of the molecular structure, such as the nature of the short-range fold, the plane of folding and the precise arrangement of the chains

within the molecule, remain unresolved. (Perutz :1949b:492)

He noted that the polypeptide chains in haemoglobin were probably like those in α -keratin, and the model proposed was similar to that put forward by Astbury and Gorter in their pre-war study of protein monolayers. Recently Perutz has noted:

I had completely fallen in love with the model of folded parallel rods and this was proved completely false in the end. It was based on 3D Patterson analyses. Crick eventually showed me that the arguments for this were qualitative rather than quantitative. (Perutz :1970c:3)

Bragg commented in the following manner:

For a long time the idea that the molecule contained some kind of regular structure of protein chains, which would give a strongly defined character to a Patterson synthesis was a guiding star which encouraged the investigations. As events turned out, it was a false star. Of the alternatives (the more complicated) is now known to be correct. If this had been realized at the time the problem would have seemed so hopeless that the quest might well have been discouraged, but fortunately this was not the case. (Bragg W.L. :1965c:4)

9.3 The α -Helix

Bragg has written:

I began to get deeply interested in Perutz's results at this stage and speculated on the form of the folded polypeptide chain. It seemed to me that Astbury's model of a kind of Greek key pattern was extremely improbable, and that a helix was a far more likely structure because it placed each amino-acid residue in the same kind of position in the chain. (Bragg W.L. :1965c:6)

The result of this was a joint paper (Bragg W.L., Kendrew and Perutz ;1950) which was an exploration of possible helical structures for the polypeptide chain.¹ They went through a complete catalogue of types, finding that none were completely satisfactory. They summarised the principles of the model-building approach in the

1. The idea that the α -structure was helical was not original having been discussed by Huggins in 1943.

following:

Astbury's studies of α -keratin, and X-ray studies of crystalline haemoglobin and myoglobin by Perutz and Kendrew, agree in indicating some form of folded polypeptide chain which has a repeat distance of about 5.1A, with three amino-acid residues per repeat. In this paper a systematic survey has been made of chain models which conform to established bond lengths and angles, and which are held in a folded form by N - H - O bonds. After excluding models which depart widely from the observed repeat distance and number of residues per repeat, an attempt is made to reduce the number of possibilities still further by comparing vector diagrams of the models with Patterson projections based on the X-ray data. When this comparison is made for two-dimensional Patterson projections on a plane at right angles to the chain, the evidence favours chains of the general type proposed for α -keratin by Astbury. These chains have a dyad axis with six residues in a repeat distance of 10.2A, and are composed of approximately coplanar folds. As a further test, these chains are placed in the myoglobin structure, and a comparison is made between calculated and observed F values for a zone parallel to the chains; the agreement is remarkably close taking into account the omission from the calculations of the unknown effect of the side-chains.

(Bragg W.L., Kendrew and Perutz :1950:321)

Kendrew saw this paper as striking off from the main line -he felt that it was foolish to concentrate exclusively on protein crystallography (Kendrew :1970a:6). Perutz was rather more explicit:

I had not done any model building previously, and took to it rather slowly. The paper was ill planned because nobody had looked at the chemical properties of amide groups. We should have studied stereochemistry more, but instead we just barged in and built models. Our ideas all came out of my hypothesis about the structure of haemoglobin as a bundle of parallel rods. Bragg suggested that model building could provide the solution on the basis of this hypothesis.

Because Astbury saw a 5.1A period and because my Patterson work seemed to show this, we forced our models to conform. Had we realised the true figure of 1.5A we would have got to the right conclusion. (Perutz :1970c:5)

Bragg, quite simply, said:

I have always regarded this paper as the most ill-planned and abortive in which I have ever been involved. (Bragg :1965c:7)

After this unsuccessful work, Pauling, Branson and Corey (:1951) developed a convincing hypothesis for the structure of the α -helix in 1951. This marked an advance on two fronts. Firstly, for

obvious reasons the proposal simplified problems of protein structure. The α -chain structure had preoccupied all those concerned with proteins since 1930. Astbury advanced two models, and many others had also postulated structures. With Pauling's work, the problem of the fibrous proteins was in essence solved, and at the same time the problems of crystalline protein structure were at least simplified. Even so, reactions to the new structure were somewhat mixed. Bernal was not immediately convinced, partly because he knew that there was no trace of a 1.5Å repeat in Carlisle's work on ribonuclease (Perutz :1970c).¹

Secondly, the crystallographic implications of this work were also important. Bernal has written:

(These ideas) required very large modifications of the basic ideas of crystallography. These ideas had contained the restriction that a helix was possible in crystals only with a helicity of 2-, 3-, 4-, and 6- fold symmetry, the screw axes of elementary space-group theory. It was not a new idea, by any means, that the peptide chain should be helical, but this limitation appeared much too stringent to account for the variety of protein structures. In fact there was no real reason why the crystallographic limitation of symmetry should apply to the internal structure of a molecule. It only strictly applied to relations of separate molecules in the same cell. The stroke of genius on the part of Pauling was to abandon the idea of integral repeats along a helix and to substitute a helix of peptides with an irrational and, therefore, not exactly repeating structure. (Bernal :1968a:373)

Kendrew has described this publication by Pauling in 1951 as a "bolt from the blue" (Kendrew :1970a:7), while Perutz reacted in the following way:

The Proceedings of the National Academy arrived containing Pauling's four papers. I read these on Saturday morning, and I was so furious that I had missed the solution that I immediately saw that the regular arrangement should give a 1.5Å repeat -- which Astbury and the other synthetic polypeptide workers should have noticed, but never reported. I worked out why

1. Pauling, however, like most other workers of the period, assumed that the α -helix was a more important part of the globular proteins than in fact turned out to be the case (Bernal :1969a:375).

Astbury could not have found these observations due to the particular features of his technique. I rushed to the lab. with a bunch of horsehair from a mattress or something -- I photographed this, and the reflection was there. I also tried this with various other materials, and, in collaboration with Huxley, on muscle. (Perutz :1970c:4)

Perutz' paper was short but conclusive (Perutz :1951a). The new reflection was found by:

oscillating the specimens about a direction normal to the fibre axis, so as to satisfy Bragg angles for planes perpendicular to that axis, and by taking photographs in cylindrical films of 3- cm. radius instead of the flat planes normally used.

(Perutz :1951a:1053)

The discovery of the 1.5A. spacing effectively ruled out all the other hypotheses about the α - structure, while it accorred with that of Pauling. However, in a second paper, Huxley and Perutz noted that:

Our results are incompatible with the mechanism of muscle contraction proposed by Pauling and Corey, who suggest that chains in extended muscle are almost fully stretched, and that they coil up to form 3.7A residue helixes on contraction. On the other hand, our findings are in accord with those of Astbury and Dickinson, who showed both extended and relaxed muscle to have the α -keratin structure which becomes disorientated on contraction. (Huxley and Perutz :1951:1054)

9.4 The "Transform" Methods

Two papers on the external shape and packing of haemoglobin were written in 1952 (Bragg W.L. and Perutz :1952a; 1952b). In the first the molecules were found to be 65 or 80A. by 55A. by 55A. This was deduced by the scattering variations brought about by changing the density of the salt solution in which the protein molecules were bathed. In the second paper they suggested that haemoglobin was ellipsoid in shape. Bragg has noted that although the results of these two papers were modest, they were none the less "noteworthy as being the first definite quantitative piece of

knowledge to be won" (Bragg :1970a:184). Perutz, too, looks upon these papers as having passed the test of time (Perutz :1970a:184).

Next Perutz and his collaborators turned to the "transform" method. As this is rather technical and inaccessible, Bragg's semi-technical description will be quoted at length:

The projection of the monoclinic crystal along the b axis has a centre of symmetry, and therefore the phases of the diffraction beams in the b plane of the reciprocal lattice are + or -. If the signs of all these spots are known, a projection of the molecule on the b plane can be formed. The next step was to go as far as possible in determining these signs by using a peculiar feature of the shrinking and swelling of haemoglobin crystals During this process the a axis, and the b axis ... remain constant, indicating that the molecules in sheets in the ab plane do not alter their relative positions. The c axis remains approximately constant, and the main change is in the angle β Since a remains constant, all spots appear on the same set of (reciprocal) layer lines, but the position of the spots on these layer lines is different for each shrinkage stage. Perutz laboriously measured the absolute F values for each stage. When plotted on the same diagram their values outline a series of nodes and loops, because they represent sections of the molecular transform which passes through a zero value when changing from + to -. (In one particular case) ... it is possible to give + and - signs to the successive loops, because one starts with the knowledge that the central peak is positive. Knowing these signs, one can form a Fourier series which gives the projection of the electron density of the protein molecule on the c axis, ...
(Bragg W.L.:1965c:8)

Once the sign of a single F value is known, it is easy to determine the signs of all the other values on the same layer line.

The first paper in the series (Bragg and Perutz :1952c) described an initial exploration of the method, and gave electron density projections only along the c (ie reciprocal lattice) axis. It none the less led to the undermining of the parallel fold theory of haemoglobin structure. Bragg and Perutz wrote:

It appears certain that the molecule is a far more complex entity than a simple picture of sheets of parallel chains would suggest. The projection on c^* which has been described in the present paper is deceptively simple. The nodes and loops of the complete ($h0l$) transform, on the other hand, have a highly complex distribution, ... (Bragg and Perutz :1952c:434)

The parallel rods model had already come under attack from Crick on technical grounds.¹ Olby (:1970a:938) has written that in 1950

Crick:

gave a seminar on his conclusions which he titled, on the advice of Perutz's co-worker John Kendrew, "What Mad Pursuit". Perutz, Kendrew, and Bragg listened while this newcomer exposed the inadequacies of their techniques and attacked their picture of the haemoglobin molecule ...

Crick believed that the technique of counting vectors so far employed was too superficial, and since a three dimensional structural analysis was prohibitively lengthy, he tried reducing this to a two dimensional analysis in the direction of the rods. This exercise, which he completed some time after his seminar talk, revealed a tenfold discrepancy between the model and the diffraction data. Crick concluded that only half the protein in the molecule could be arranged in the manner of the hat box model. He believed that there were more kinks, shorter straight runs, and that even when broadly parallel the chains meandered. (Olby :1970a:948)

This talk, and the subsequent work by Crick, showed that the regular folded chain model postulated by Perutz was much too simple.

Olby quotes Crick as saying:

It is one of the occupational hazards of the sort of crystallography in which you do not get results within a reasonable time, that those who work in it tend to deceive themselves after a bit; they get hold of an idea or an interpretation and unless there is someone there to knock it out of them, they go on along those lines, and I think that that was the state of the subject when I went to the Cavendish. (Crick, quoted by Olby :1970a:949)

Kendrew and Perutz took this attack on their methods very well, but Bragg was less pleased, and told him after the meeting:

Crick! You are rocking the boat! (Crick:1971)

Obviously Crick had very seriously rocked the boat -- he had undermined the whole approach which he had shown to be qualitative and not quantitative. It is not surprising, therefore, that Bragg and

1. Crick was a physicist who came to the MRC Unit by way of a two year studentship at the Strangeways Laboratory, and had read his way into X-ray crystallography. R.Olby has made a detailed study of Crick's scientific career (Olby :1970a:938).

Perutz were cautious in interpreting the results of the transform paper published in 1952. In fact, they as good as withdrew the parallel rods model.

The second paper in the series was on the size of the haemoglobin molecule. Knowledge of the size was required if any serious progress was to be made with the transform method. In the earlier paper Bragg and Perutz had noted:

Whatever the arrangement of the scattering points in the structure, the maxima and minima (of the transform) succeed each other with a certain minimal distance of separation, or minimal wave number, which depends upon the overall dimensions of the molecule in a corresponding direction.

(Bragg W.L. and Perutz :1952c:428)

In the new paper (Bragg W.L., Howells and Perutz :1954) more detailed data about the external shape of the molecule was reported. The relative signs of a number of layer lines were established by means of the transform method and the minimum wavelength principle.

In the third paper (Perutz :1954a) the transform method was extended to include the $h0l$ reflection. Although the method was very limited, it was producing some relatively successful results. Unfortunately, however, it was not always possible to establish whether there was a node in the transform, and the absolute signs for layers where h was greater than two had not been determined. The method was shortly to be superseded by the isomorphous replacement method. Thus, Perutz wrote:

The uncertainties left by the transform method have now been cleared up with the help of two further methods of sign determination. The first is based on a comparison of several isomorphous forms, one being pure haemoglobin and the other compounds of haemoglobin with heavy metals. The second method uses an apparently orthorhombic compound of haemoglobin with imidazole. (Perutz :1954a:264)

Papers on all of these methods were published simultaneously in

1954.¹ In the paper on the transform method Perutz plotted out the results from both a salt and a salt-free transform. In a concluding section of the paper he discussed the value of the transform method:

The isomorphous replacement method proved that seven mistakes in the transform plot had been made; it is doubtful that any increase in experimental accuracy, or in the number of lattice stages examined, would have further reduced this number. Addition of the seven mistakes to the uncertain signs of six layer lines brings the total number of ambiguities to 13. This result can be regarded in two ways. It implies about 8200 alternative Fouriers, which shows that it is impossible to solve the structure by the transform method alone. On the other hand, the result also implies that only thirteen additional signs are now required for a unique solution. Thus the large number of sign relations implicit in the transform allows the validity of any independent sign determining method to be checked, and this fact has proved to be of the greatest assistance in solving the problem. (Perutz :1954a:285)

This paper marks the culmination of a major effort to determine the signs of the reflections by means of the transform method. Bragg's conclusion about the method was that it provided:

a reliable fragment of information, though so meagre, and we snatched at such small successes to keep ourselves in heart to carry on with the investigation. (Bragg W.L. :1965c:10)

9.5 The Isomorphous Replacement Method

Perutz was alerted to the possibility of isomorphous replacement in haemoglobin by work carried out in 1952 by Riggs, who showed that human haemoglobin combined with two molecules of para-chloromercuribenzoate. It is a legitimate question to ask why the heavy atom method had not been attempted before, in view of the fact that it was a classical crystallographic technique (Kendrew :1970a:9).

1. Green, Ingram and Perutz :1954; Howells and Perutz :1954; Bragg and Perutz :1954.

As was mentioned earlier, in 1939 both Bernal and Robertson suggested that the method might be applied to proteins, and Hodgkin worked on it during her period of postgraduate study at Cambridge, although this was not on proteins. Robertson's work developed the technique in the thirties, and Bijvoet, a Dutch crystallographer, who solved the structure of strychnine in 1948, developed the phase lag method, in which the phase angle is determined even where the heavy atom is not at a centre of symmetry. Hodgkin was also responsible for several important developments, and had used the isomorphous replacement method to determine the structure of chloesterol iodide and calciferyl-4-iodo-nitrobenzoate in the late fourties. In the early fifties she was actively studying Vitamin B 12. Yet, despite all this work, the study of heavy atom methods in protein crystallography did not start seriously until 1952.

There were two main reasons for this -- reasons that were briefly mentioned in Chapter Seven. Firstly, it was considered doubtful whether the phase contribution of the heavy atoms would be sufficient to allow phase angle determination. The second reason was chemical. Not only was it difficult to make heavy atom derivatives of proteins, but it was also far from clear that the heavy atoms would settle down at particular discrete spots, and thus allow the method to work. Perutz outlined the difficulties by noting that in the past it had been thought that:

the difference in intensity to be expected from the attachment of heavy atoms would appear to be hardly larger than the sum of the errors in two separate measurements. In fact, however, the r.m.s. amplitude per molecule is only 300, much smaller than would be expected on statistical grounds. In consequence the contribution of heavy atoms can be detected and measured.

(Green, Ingram and Perutz :1954:288)

In the very early fifties, Riggs discovered that human haemo-

globin combined with para-chloromercuribenzoate (reacting with the sulphhydryl groups of cysteine) without affecting the reversible combination of haemoglobin with oxygen. This implied that the molecular structure was not radically altered by the attachment. However, even so, the problem was not solved, because Riggs' work had been carried out on human haemoglobin, which was a system unsuitable for X-ray diffraction studies. In the paper the authors wrote:

We found native horse oxyhaemoglobin to react with para-chloromercuribenzoate and with silver ions. When stoichiometric proportions of two molecules of reagent to one molecule of haemoglobin are used, the compounds so formed are readily crystallized, and the crystals are isomorphous with the normal monoclinic form of horse oxy- or methaemoglobin.

(Green, Ingram and Perutz :1954:289)

There was a division of labour between Perutz and Ingram.

Perutz was responsible for the development of the physical aspects of the new technique, while Ingram worked on the chemistry. Both Perutz and Kendrew relied heavily on Ingram's expertise (Kendrew :1970a:9), as the chemical techniques were very difficult.^{1 2} However, although the chemical work was important, Perutz' own contribution was vital:

Perutz' triumph (was) his expertness in measuring the strength of the spots on the photograph so that he could estimate to a

1. There was more trouble preparing isomorphous derivatives for myoglobin than haemoglobin. The -SH groups in haemoglobin permitted easy attachment of heavy atoms, while there were no such groups available in myoglobin. They tried a number of different methods in myoglobin, resulting in the end in the use of what Kendrew has described as "semi-empirical" methods.

2. In the fifties this sort of division of labour increased -- a fact that can be seen from the large number of names attached to the published papers. Work was done on a team basis, as chemical, measurement, and computing tasks all became larger.

sufficient accuracy the changes in F produced by the heavy atom. In this last his skill was at that time probably unique.
(Bragg W.L. :1965c:12)

The intensities of the two derivatives were compared with those of the unsubstituted unit cell, and a "difference Patterson" was calculated.¹ In this way the position of the two mercury atoms was determined. However, the authors went on:

The difference Patterson does not fix uniquely the position of the mercury vector relative to the centre of the haemoglobin molecule. The vector may be centred on each of the dyads and screw dyads in the unit cell, giving eight pairs of possible mercury positions for the two molecules in the unit cell.
(Green, Ingram and Perutz :1954:300)

By examining the unit cell, and the known shape of the molecule, three of the eight pairs of possibilities were eliminated. By looking at the changes caused by the mercury in the intensities of the four reflections of known sign further regions of the unit cell were excluded. This left only one pair of positions, and made it possible to calculate the structure factors.

The results proved to be consistent with those of the other methods, and the signs of most of the loops were determined.

Perutz and his colleagues noted that:

This is a remarkable result. It is worth emphasizing that it was achieved, as it were, automatically, without any need to eliminate inconsistent signs by post facto checking of intensity readings which might have been influenced by subjective judgement. During the measurement of the X-ray photographs it is impossible to know whether an increase or a decrease in a particular intensity is required to give a consistent answer. It is all the more impressive when, after a week's calculation without any idea as to what the final result would be, the signs are finally worked out and found to form a consistent set.

(Green, Ingram and Perutz :1954:306)

1. A difference Patterson makes use of the difference between the intensities of reflection in two or more isomorphous compounds, being calculated from the square of the difference of the structure factors. The result of a difference Patterson is to reveal the vector that lies between the heavy atoms.

The third paper (Howells and Perutz :1954) discussed the imidazole-methaemoglobin crystals, which also offered an independent check on the signs of the loops determined by the isomorphous replacement method.

In the fourth paper (Bragg W.L. and Perutz :1954) the Fourier transform that had been measured in the preceding papers was used to calculate an electron density projection in the 010 plane. The authors wrote:

The structure of haemoglobin is a structure of much greater complexity than any other yet attacked by X-ray analysis. Some tentative solutions of the structure have been proposed in the past, but it has been impossible to prove them either right or wrong. What is novel in the present attack on the problem is the certainty of the results. The proof of their correctness, however, is different from that offered in the crystal-structure analysis of compounds where single atoms can be resolved. In those simpler structures proof rests on agreement of the atomic positions with the known facts of stereo-chemistry and with the observed intensities of the diffracted rays. The picture of the haemoglobin molecule which now emerges from the Fourier projections cannot yet be interpreted and contains only few features that can be recognized as intrinsically right. Its proof rests entirely on the agreement between the different sign determinations described in the preceding papers in this series. (Bragg W.L. and Perutz :1954:315)

There were two problems that prevented the interpretation of the electron density projection. Firstly, resolution was so low that point atoms were spread out over an area of up to 9A. diameter in the map. The obvious way to overcome this was to include the signs of higher order reflections. The second problem resulted from the fact that a great depth of material was projected. In most parts of the map there were probably thirty or forty overlapping atoms.

After this calculation, they noted that the hat box model was incorrect, and the molecule appeared to be a tilted spheroid of dimensions 71 by 54 A.:

The internal structure of the molecule is still obscure. There are no regularly spaced layers; the deceptive regularity of the seven peaks in the one-dimensional Fourier is purely accidental in origin. As to the three-dimensional Patterson and the tentative Fourier projection on the a plane which indicated a regular arrangement of parallel polypeptide chains in at least part of the molecule, the present results contain nothing that would either prove or disprove that interpretation. Much greater resolution is evidently required, and there is no reason why this should not be obtained.

(Bragg W.L. and Perutz :1954:326)

Bragg has written about the implications of the above work:

The b projection was a big step forward, but still told disappointingly little about the structure of the protein molecule, since the features of a structure 50Å in thickness are hopelessly confused in the projection. It was clear that a three dimensional analysis would be necessary. Such an analysis presents still more formidable problems. In the b projection, signs + or - are alone required and an accuracy sufficient to make the right choice is all that is needed. In three dimensions, phases which may have any value between 0 and 2π are necessary. The accuracy with which phase could be determined for a diffracted beam depended on the accuracy of determination of changes in F . The great question which exercised us at this stage was 'Could heavy atom substitution be used in practice to get sufficiently accurate phases?'

(Bragg W.L.:1965c:14)

9.6 Myoglobin

It is perhaps a little ironical that myoglobin rather than haemoglobin was the first protein to be solved. In fact, Perutz and Kendrew worked together and shared a room. Their collaboration was extremely close (Perutz :1970c:6)

Kendrew, who joined Perutz after the war, chose to work on myoglobin for a number of reasons. Firstly, it was important to choose a protein that would crystallise easily. Secondly, it was better if it had a low molecular weight, as this would make the structure determination easier. Thirdly, he sought a protein that was not already being worked on by another crystallographer. Fourthly, it seemed likely that there would be similarities between

myoglobin and haemoglobin, for although the former is much smaller, they both combine reversibly with oxygen (Kendrew :1970a:2; 1969a:2).

Although myoglobin was convenient for X-ray diffraction, the commoner varieties from domestic animals proved difficult to crystallise, and in the late forties Kendrew examined myoglobin from a number of different species. This work was reported in 1954 (Kendrew, Parrish, Marrack and Orlans :1954) when twelve different types were investigated, both by crystallographic and immunological means. Aquatic animals were specially sought, as they were rich in myoglobin. Kendrew chose to do his main work on sperm whale myoglobin, although he later organised a team at the Royal Institution which worked on seal myoglobin. The Low Temperature Research Station at Cambridge did a great deal of research on whale meat during the war, while searching for food substitutes, and they happened to have large stocks of whale meat which provided an excellent source of crystals (Kendrew :1970a:10).

Kendrew's work ran parallel to that of Perutz. As has been noted elsewhere, Kendrew was responsible for development of several labour-saving techniques. He was the first crystallographer in Cambridge ¹ to learn computer programming, although neither Bragg nor Perutz at first believed the answers produced by the machine, EDSAC I. It was at an experimental stage when he first started using it (Kendrew :1970a:4) and as its valves were always failing it frequently broke down. He also developed an optical densiometer

1. It seems probable that he was one of the first crystallographers to learn computer programming.

which proved to be extremely important in intensity measurements.¹

In 1958, the structure of the first crystalline protein, that of sperm whale myoglobin, was determined. In the paper² the authors discussed Perutz' work on haemoglobin, mentioning the technique of isomorphous replacement. They noted that Perutz had attached a molecule of para-chloromercuribenzoate to each of the free sulphhydryl groups in haemoglobin. They went on:

No type of myoglobin has yet been found to contain free sulphhydryl groups, so that the method of attaching heavy atoms used by Perutz for haemoglobin could not be employed. Eventually, we were able to attach several heavy atoms to the myoglobin molecule at different specific sites by crystallising it with a variety of heavy ions chosen because they might be expected, on general chemical grounds, to possess affinity for protein side-chains. X-ray, rather than chemical, methods were used to determine whether combination had taken place, and, if so, whether the ligand was situated predominantly at a single site on the surface of the molecule. (Kendrew et al :1958:662)

They located the heavy atom by carrying out a Patterson difference synthesis, and then, knowing the position of the heavy atoms, they calculated an electron density projection along y. Unfortunately this was uninterpretable as too many features were superimposed upon one another. Next, the x and z co-ordinates of the heavy atoms were determined, and these were used as a starting point for the three dimensional analysis. They wrote about the latter:

In three dimensions the procedure is much more lengthy because all the general reflexions hkl must be included in the synthesis, and more complicated because these reflexions may have any relative phase angles, not only 0 or π .
(Kendrew et al :1958:663)

In addition, it was difficult to determine the y co-ordinate of

1. Kendrew's work between 1948 and 1958 will not be described in detail, as all the more important technical advances and problems have already been mentioned in the account of Perutz' work.

2. Kendrew, Bodo, Dintzis, Parrish, Wyckoff and Phillips :1958; henceforth called Kendrew et al :1958'.

the heavy atoms. Even when this was achieved there was still a formal ambiguity which necessitated the study of several, and not just one isomorphous replacement. Knowing the phases, a three dimensional Fourier synthesis was calculated. However:

Before such a programme is embarked upon, however, the resolution to be aimed at must be decided. The number of reflexions needed, and hence the amount of labour, is proportional to the cube of the resolution. To resolve individual atoms it would be necessary to include at least all terms of the series with spacings greater than 1.5A -- some 20,000 in all; and it is to be remembered that the intensities of all the reflexions would have to be measured for each isomorphous derivative. Besides this, introduction of a heavy group may cause slight distortion of the crystal lattice; as the resolution is increased, this distortion has an increasingly serious effect on the accuracy of phase determination. In the present stage of the analysis the most urgent objective was an electron-density map detailed enough to show the general layout of the molecule -- in other words its tertiary structure. If the α -helix, or something like it, forms the basis of the structure, we need only work to a resolution sufficient to show up a helical chain as a rod of high electron density. For this purpose we require only reflexions with spacings greater than about 6 A.

(Kendrew et al :1958:663)

The synthesis was computed on Edsac Mark I and checked by DEUCE at the National Physical Laboratory. It was produced in the form of sixteen layers, perpendicular to y , just under 2 A. apart.

The molecule had a totally unexpected and irregular structure:

The characteristic of X-ray crystallography is that while you're solving the structure you have absolutely nothing. And then one day, it all comes out with a bang. And this is unlike most scientific problems. And especially the protein one, where you're working for a very long time. So, you know, it was really very exciting one Sunday morning to have this -- especially as one wasn't sure it was going to come out; and one had no idea, because it was the first one -- one had no idea what it was going to be like when it came out. So you got this picture, and you didn't even know what to expect. You didn't even know whether you would be certain it was right or wrong. I mean, maybe it would be so unrecognisable that you wouldn't know whether it was -- well, as it turned out it was, clearly it was right. Because it had very striking features which couldn't have been the result of chance, you see. Well this was certainly a very exciting moment. I can remember we calculated the thing on a Saturday night and spending Sunday morning plotting it out. And it slowly became apparent during

that Sunday morning that this was really the answer. And that this thing looked unlike anything anybody had expected.
(Kendrew :1969a:4)

Some of the areas of high electron density were identified as features that were known, or might reasonably be expected to exist, in the myoglobin molecule. The model contained "a number of prominent rods of high electron density" which ran in fairly straight lines for up to 40 Å. The rods were approximately circular in cross-section, and 5 Å. in diameter. In other places there were curved rods of high electron density, and segments of rod joined up by sharpish corners. It was almost certain that these rods represented chains of polypeptides. It seemed equally probable that a single disk of high electron density represented the haem group. There were four reasons for this. Firstly, the haem group was known to be a flat disk of about the right size. Secondly, it was known that there was an iron atom at the centre of the haem group, and there was indeed, an appropriate area of very high electron density. Thirdly, so far as could be determined by a difference Fourier synthesis, the one ligand that was known on chemical grounds to have an affinity for the haem group was located in the correct position. Fourthly, the orientation of the haem group from the electron density map was in conformity with that produced by electron spin resonance studies.

The outline shape of the molecule was determined by assuming that there were no high density bridges between adjacent molecules. Although this contained a number of small ambiguities, it was confirmed by the salt water difference-Fourier previously carried out to determine the outline shape of the molecule.

In conclusion, the authors wrote:

Perhaps the most remarkable features of the molecule are its complexity and lack of symmetry. The arrangement seems to be almost totally lacking in the kind of regularities which one instinctively anticipates, and it is more complicated than has been predicated by any theory of protein structure. Though the detailed principles of construction do not yet emerge, we may hope that they will do so at a later stage of the analysis. We are at present engaged in extending the resolution to 3A., which should show us something of the secondary structure; we anticipate that still further extensions will later be possible -- eventually, perhaps, to the point of revealing even the primary structure. (Kendrew et al :1958:665)

A two dimensional electron density projection of seal myoglobin was published by Scouloudi of the Royal Institution in 1959 (Scouloudi :1959). Then, in 1960, Kendrew published a three dimensional Fourier synthesis of sperm whale myoglobin at 2 A.¹

The work represented an extension by the same methods:

Whereas myoglobin crystals give 400 reflexions having spacings greater than 6A., the number of reflexions with spacings greater than 2A. is 9,600, each of which has to be measured not only for the unsubstituted protein but also for each of the derivatives. The very much greater number of data posed many problems, both in recording intensities and in computation, and in this stage we relied much more heavily than before on the use of a high speed computer; it was fortunate that about the time the work began the Edsac Mark I computer used previously was superseded by the very much faster and more powerful Mark II. (Kendrew et al :1960:423)

Because of the high resolution, direct proof of the presence of the α -helix was obtained. There was a low electron density core down the centre of each rod of high density, and the helices were found to be right-handed. Between 100 and 110 out of 153 residues were in the α -helix form. Plausible models for some of the sharp corners in the polypeptide chain were constructed, and in a few cases the direction and nature of an amino-acid side-chain was determined. The tilt of the haem group was found to be 21° out

1. Kendrew, Dickerson, Strandberg, Hart, Davies, Phillips and Shore :1960; referred to hereafter as Kendrew et al :1960.

of the bc plane, but in the opposite direction to that proposed in the first model.

In 1961, the analysis of myoglobin was carried a stage further¹ with an X-ray and chemical study of the amino-acid sequence in myoglobin. The authors wrote:

Interpretative techniques have now been improved ... and it has in fact proved possible to identify many side-chains with assurance, and in many other to narrow the choice to two or three. To determine completely the amino-acid sequence of a protein by X-ray methods alone, it will clearly be necessary to work at higher resolution than 2 Å. ... ; but in the meantime it has been possible, by correlating the present X-ray identification with the preliminary chemical results, described in the preceding article by Edmundson and Hirs, to arrive at a tentative amino-acid sequence which though it is incomplete and contains ambiguities and no doubt some errors, cannot be very far from the truth.

(Kendrew et al :1961:666)

Reasonable agreement was found between the data reported in this paper, and that reported by Edmundson and Hirs (:1961) obtained by chemical means. The third paper, by Watson and Kendrew (:1961), compared the amino-acid sequence of sperm whale myoglobin with that of human haemoglobin². Perutz had showed that there were similarities between the tertiary structure of the two halves of haemoglobin and that of myoglobin³. Watson and Kendrew wondered whether, despite amino-acid differences, there were physical similarities which accounted for the similar properties. They noted that:

1. Kendrew, Watson, Strandberg, Dickerson, Phillips and Shore :1961; referred to hereafter as Kendrew et al :1961; Watson H.C. and Kendrew :1961; Edmundson and Hirs :1961.

2. The latter was determined by chemical means, by Hill and Konigsberg.

3. This work is reported in the following section.

The main impression is that in spite of presumed resemblances in the tertiary structure, the correspondances are remarkably few. It must be concluded from this and the preceding article (Kendrew et al :1961) that the crucial interactions which determine the tertiary structure of a protein are very complicated and are not confined to the corners between helices; detailed investigations, perhaps including comparisons between related proteins, will be necessary before general principles become apparent. (Watson H.C. and Kendrew :1961:672)

9.7 Haemoglobin

In 1960, Perutz published a low resolution electron density map of haemoglobin ³. Six different isomorphous replacements were used, and a difference Patterson was used to locate the heavy atoms. The results were plotted on an electron density map, with a resolution of 5.5Å. The size of the molecule calculated in this way was found to agree with previous estimates, and the orientation of the haem groups was confirmed with previous electron spin resonance work. The authors noted:

Clearly, the four tortuous clouds of high electron density in haemoglobin represent the four polypeptide chains. The black and white chains have similar but not identical configurations. (Perutz et al :1960:418)

By comparing the model of haemoglobin with the more detailed model of myoglobin discussed above, sections of α -helix were identified. Finally the authors wrote that:

(The appearance of the folds in the polypeptide chain) in horse haemoglobin suggests that all haemoglobins and myoglobins of vertebrates follow the same pattern. How does this arise? It is scarcely conceivable that a three-dimensional template forces the chain to take up this fold. More probably the chain, once it is synthesized and provided with a haem group around which it can coil, takes up this configuration spontaneously, as the only one which satisfies the stereochemical requirements of its amino-acid sequence. (Perutz et al :1960:421)

1. Perutz, Rossman, Cullis, Muirhead and North :1960; referred to hereafter as Perutz et al :1960.

The final set of papers on haemoglobin that will be discussed here are those that presented the 2.8 Å. three dimensional Fourier synthesis of horse haemoglobin in 1968¹. In the first, the method and calculations were outlined. By 1968 techniques had advanced beyond those available for the earlier work reported above, and the three circle diffractometer (designed by Arndt) which recorded its output on punched tape was used. The calculations were done by computer. The authors wrote:

The results which emerge from the present Fourier synthesis are remarkably clear. Although the electron density maps by themselves would not suffice to solve the structure, when combined with the chemical sequence and the known stereochemistry of the amino-acids they provide enough information for the construction of an atomic model. (Perutz et al :1968a)

In the second paper it was noted that physical model building even when carried out with the greatest care, none the less resulted in excessive inaccuracy. For this reason, mathematical model building was used. In the Croonian Lecture (Perutz :1969a) Perutz noted:

... the general principles of construction appear to be such as to lead to the least free energy and the greatest possible entropy of the protein molecule and its surrounding water.
(Perutz :1969a:135)

9.8 The Achievement of Success

The work that led to the determination of the structure of haemoglobin and myoglobin constituted a single-minded attack on a difficult scientific problem. For both Perutz and Kendrew it was undoubtedly a major triumph. Kendrew's excitement on the day when

1. Perutz, Muirhead, Cox, Goaman, Mathews, McGandy and Webb :1968; referred to hereafter as Perutz et al :1968a; Perutz, Muirhead, Cox and Goaman :1968; referred to hereafter as Perutz et al :1968b; Perutz :1969a.

the 6 Å. map was calculated was mentioned above. Perutz, too experienced his moments of triumph:

Interviewer When you make a discovery of this kind, is there a moment of truth -- a day, or a moment when you suddenly find out you've made a discovery?

Perutz Oh, there is indeed. You know, it is really this moment the scientist lives for; it is the most exciting thing that can happen to you. It is like falling in love, discovering a new continent and winning a great victory, all in one. You jump out of your skin when you suddenly see the thing in front of you which you have been wanting to know for so long. And I think it is a much greater moment than winning the Nobel Prize. You see something which no man has ever seen before, something you have been waiting and hoping for, and there suddenly it is. You're suprised and you say to yourself "My God" -- you could have guessed it must be like that.

Interviewer Can you describe to me when this was, what was this particular discovery that gave you this revelation?

Perutz Well, there were three occasions -- one, and perhaps only a minor one in 1951, when I discovered the new effect which proved that a theory proposed by an American colleague was right, and then there was 1953, the heavy atom, and introducing a heavy atom into protein crystals and suddenly realising that this was the method by which the structure of it could actually be solved. And again, in 1959, watching the structure of haemoglobin come out. So these were really the greatest highlights of my life. (Perutz :1962a:27)

Although the work represented a crystallographic triumph, like many scientific advances it created a whole new series of problems that have yet to be solved. Two of these are really disappointments for the crystallographers, since it seems likely that they hoped that with the determination of the protein structures, these problems, too, would be solved. The first concerns the relationship between structure and function. Nature noted:

This difference of opinion over whether the functional unit of haemoglobin is a dimer or a tetramer underlines the greatest disappointment of the determination of the structure of oxyhaemoglobin. Unlike the X-ray crystallographic determinations of the structure of enzymes, such as lysozyme and ribonuclease, the elucidation of the structure of oxyhaemoglobin has not made it immediately obvious how haemoglobin works, how it binds oxygen and how haem-haem interactions are achieved.

(Nature :1968:116)

The writer went on to quote Perutz:

What we have done is merely the anatomy at the atomic level.
 Now it is necessary to advance to the physiology.
 (Nature :1968:116, quoting Perutz)

The second problem concerned the principles behind the structures of proteins. Nature wrote of the 1971 Cold Spring Harbor Symposium on Quantitative Biology:

As the tangled loops of yet more structures were revealed, the bewildering mass of information became more difficult to assimilate, and the still suprising details of active sites were looked at more and more narrowly. Anybody wanting to study protein architecture and folding in general terms will soon have more data than he can cope with.
 (Nature :1971:495)

And again:

In closing, Phillips remembered, as had successive Chairmen, how great had been the contribution of men such as Bernal, the Braggs and Pauling. The mass of new data presented at this meeting and the prospect of at least ten new protein structures per year cry for minds of similar calibre to search for underlying principles. (Nature :1971:497)

9.9 Lysozyme

D.C.Phillips worked with Kendrew on myoglobin. At the end of this work, however, the workers at the Royal Institution cut their formal ties with the Cambridge group, and started to look for another protein on which they could work. An American chemist, Poljak, came to the laboratory and carried out some experiments on heavy atom derivatives of lysozyme, and partly because of this it was decided to work on lysozyme. This work made use of new methods of automatic data collection that Phillips and Arndt had developed in the course of the work on myoglobin. Phillips noted that:

One of the main problems was felt to be taking all the measurements. This was seen as an important block, since it was felt that one ought to use the diffractometer rather than photographic techniques. (Phillips :1970:5)

There were two main problems -- those concerned with orientation and those concerned with detection. Arndt worked mainly on the latter, while Phillips concentrated on the diffraction geometry. In the conventional three circle diffractometer it was necessary to turn three handles for each measurement -- a procedure which was both very boring and time consuming. Only 100 to 200 measurements a day were made, while 10,000 were necessary:

So clearly there was considerable pressure to make it automatic. We looked at computers, and asked ourselves whether the electronics had reached the stage where it was good enough to permit automatic setting. We came to the conclusion that the answer was not quite. So we turned our minds back to a more direct control mechanism, and between us we came up with what was essentially an analogue device, where there was only one handle to turn, and furthermore it was turned an equal distance each time. (Phillips :1970:6)

Phillips was also responsible for the invention and construction of a simultaneous diffractometer:

... after turning the handle for about a month it suddenly occurred to me -- what was obvious in retrospect -- that the distance between the reflection that we were measuring, and the ones on either side, were so short that it ought to be possible to measure all three at the same time. So we spent some time modifying the commercial diffractometer that we were using, and I got Arndt to help, because he was electrically competent. Then North modified the computing.

(Phillips :1970:13)

This development cut down the amount of labour, and reduced the time required for the measurement of diffractions from six weeks to two for each crystal.

The first paper on lysozyme was published in 1962¹ alongside

1. There were important differences between the methods of heavy atom replacement used by Dintzis (who worked on myoglobin) and Poljak on the one hand, and those of Harker and some other American workers on the other. The latter were much less successful, and Phillips suggests (Phillips :1970:7) that this was because the Workers in Britain adopted a much less "dogmatic" approach, being willing to try any method of heavy atom replacement.

another, rather different solution, that had been calculated by a group at Caltech¹. The methods employed were essentially the same as those used in myoglobin. The molecule seemed to be a rough ellipsoid of 52 by 32 by 26 Å. Tracing the polypeptide chain and the positions of the disulphide bridges was not easy. The authors wrote:

This has proved to be difficult if not impossible at this stage. In comparison with the maps of myoglobin and haemoglobin at this resolution it is apparent that our map of lysozyme has a much smaller proportion of clear-cut rod-like features representing helical configurations of the polypeptide chain. This is not suprising since optical-rotatory-dispersion measurements and other X-ray evidence suggest that only 30 - 40 per cent of the polypeptide chain in lysozyme is in the form of α -helix as compared with 77 per cent in myoglobin.

(Blake et al :1962:1175)

They declined to suggest a tertiary structure until resolution had been increased and they had had the chance to consult other workers and compared findings. They referred to the Caltech article (Stanford, Marsh and Corey :1962) and noted that in comparing the two results allowance should be made for three facts: the crystals (which contained niobium) which had been used by the Caltech group were not isomorphous with the ones they had used; secondly, the Caltech analysis was based on the use of only a single heavy atom derivative and it was at 5 Å. and not 6 Å.; and thirdly, it was plotted in a different space group.

When allowance is made for these differences the two maps are found to be in satisfactory agreement with many features in common. (Blake et al :1962:1176)²

1. Blake, Fenn, North, Phillips and Poljak :1962; referred to hereafter as Blake et al :1962.

2. Corey did not press his interpretation, and it has been dropped (Phillips :1970:12).

The resolution of the map was stepped up to 2 Å. in 1965.

In this work a number of new isomorphous replacements were used, as only one of the three that had been employed at the 6 Å. stage was suitable. Blake and Koenig, the chemists in the team, examined between fifty and one hundred before finding an adequate number of suitable derivatives. That the 2 Å. level considerable interpretation proved possible:

At this resolution atoms are not expected to appear in the image as separate peaks of electron density, but groups of atoms connected only by ionic or van der Waal's interactions or by hydrogen bonds are expected to be resolved. It is satisfactory therefore to find a continuous ribbon of high density with characteristic features at regular intervals to represent the main polypeptide chain with its carbonyl groups and with side-chains protruding from it. (Blake et al :1965:758) ¹

The course of the main-chain was described, and the amino-acid composition was determined by X-rays, and compared with the results previously obtained by biochemical methods. The most noteworthy feature of the molecule was a cleft which ran down one side. In a second paper (Johnson and Phillips :1965) an X-ray study of the structures of some inhibitor complexes that became attached to the cleft was made. In this way they were able to locate the part of the molecule that appeared to be responsible for its enzymic action. This paper marked a satisfactory initial attempt to understand enzymic activity by means of X-ray diffraction methods.

9.10 Hodgkin

Hodgkin's post war work has previously been mentioned, but not discussed. Her strategy was to work from simpler to more

1. Blake, Koenig, Mair, North, Phillips and Sarma :1965; referred to hereafter as Blake et al :1965.

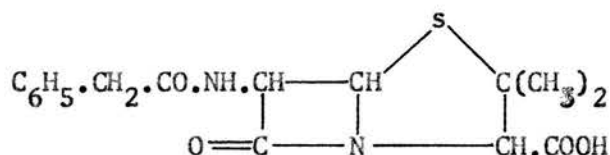
complicated molecules, using and developing the heavy atom method.

The most important of these molecules were:

1. Penicillin, on which she worked jointly with C.W.Bunn during the war.
2. Chloesterol iodide, which she determined with Carlisle, in 1945.
3. A calciferol derivative, calciferyl-4-iodo-5-nitrobenzoate, which she determined with Dunitz in 1948.
4. Vitamin B 12, published in 1957, with many collaborators.
5. The structure of insulin, published at high resolution in 1969. ¹

Robertson wrote of the penicillin work:

The power of the X-ray method in aiding the organic chemist to elucidate a difficult and completely unknown structure was perhaps first most conclusively demonstrated in the work on penicillin during the war years, when computing methods were still primitive and laborious. The formula for benzylpenicillin



may not now appear to be unduly complicated, but the chemistry is extremely difficult and unusual. The analysis was finally achieved through the rubidium, potassium and sodium salts, which are not all isomorphous. A feature of the work was the close collaboration at every stage between the crystallographers and the chemists. The final result establishes the intricate spatial relationship of the atoms in full detail, and, as is well known, has led to profound advances in the fields of chemistry and medicine. (Robertson :1962a:163)

Heavy atom methods were also used in the work on chloesterol iodide, and the calciferol derivative mentioned above. The work on penicillin was conducted in the absence of detailed chemical know-

1. Adams, Blundell, Dodson, Dodson, Vijayan, Baker, Harding, Hodgkin, Rimmer and Sheat :1969; referred to hereafter as Adams et al :1969.

ledge, and the work on chloresteryl iodide was similarly in advance of biochemistry. Bragg has written of the work in the following manner:

In the organic field, most determinations of structure had hitherto confirmed the structural models of the organic chemist. Now a very difficult kind of 'sound barrier' began to be passed, that of telling the organic chemist something he did not already know.

I may perhaps select the determination of the structure of chloresteryl iodide by Carlisle and Crowfoot (Mrs Hodgkin) in 1945 as an early example of such an achievement. Bernal's studies of the sterols in 1932 had given some indications of their structure, and in the interval the chemical nature of the sterol structure had been largely established by the organic chemists. Carlisle and Crowfoot, starting with clues to the phases indicated by the heavy iodine atoms, were able to fix the positions of the thirty-three carbon atoms in the asymmetric molecule, and so establish the sterol skeleton with precision. (Bragg W.L. :1962b:130)

The work on Vitamin B 12 was even more important ¹:

In the field of complex molecules the most outstanding example during this decade has undoubtedly been the complete solution of the structure of Vitamin B 12 by D.C.Hodgkin, J.G.White and their many collaborators. Furthermore, this feat was accomplished during the early years of the period, and before computing methods had nearly reached their present state of high efficiency. As a complete structure determination it can still be considered (1962) the crowning triumph of X-ray crystallographic analysis, both in respect of the chemical and biological importance of the results and the vast complexity of the structure.

The formula, $C_{63}H_{88}O_{14}N_{14}PCo$ together with about 24 molecules of water, shows that, even without counting hydrogen, there are about 350 positional parameters to determine. The cobalt atom is far too light for anything like complete phase determination. Nevertheless, with this as a starting point, and with great determination and skill, involving what can only be described as gifted intuition at some points, the complete structure was finally elucidated.

(Robertson :1962a:165)

The work started in 1948, and gradually chemical evidence about

1. Hodgkin, Kamper, Lindsay, MacKay, Pickworth, Robertson, Shoemaker, White, Prosen and Trueblood :1957; hereafter referred to as Hodgkin et al :1957.

some of the constituent parts of the molecule became available, although nothing was known about the way these parts linked up. The X-ray methods also advanced gradually. Using the cobalt atom as a start, more and more atomic positions were approximately determined, and their positions used to calculate more accurate phase angles. In addition, other derivatives were also studied, and this contributed to the determination of more accurate phase angles. Finally, in 1957, the structure was published.

In the above work, which brought Hodgkin very high prestige in the crystallographic and chemical communities ¹ she developed skills and methods, especially in the area of heavy atom and isomorphous replacement. Her successful work on insulin published in 1969 can be seen as the culmination of this work.

9.11 Conclusion

The above ends the brief account of successful post war work on the structures of globular proteins. Although a similar effort was made at Birkbeck College under Bernal and Carlisle, no major results ever came from this team. Astbury, although he was still working in the late forties and early fifties, increasingly developed his concern with ultrastructure, studied by such methods as the electron microscope. His interests were quite unlike those of Perutz and the others discussed above.

1. This fact can be seen from Robertson's statements above, and also from the fact that she was awarded the Nobel Prize for Chemistry in 1964 for "a remarkably coherent and well planned series of investigations covering the whole field of organic structures of medical and biological importance."

10 LITERATURE REVIEW

10.1 Introduction

The tradition in the sociology of science goes back, at the very least, to the prewar work of R.K.Merton, and although the critics of Merton might argue that little progress has been made until quite recently, none the less the body of work in the Mertonian tradition is quite considerable. The plan of this review of the literature will be as follows: firstly, the work of Merton and the functionalist school, in so far as it relates to the sociology of academic science, will be mentioned. Then some recent developments, many of them in radical opposition to the position adopted by Merton in important and central respects, will be more fully discussed. The purpose of the review is, in part, to document the swing away from the functionalist understanding of science to this more recent approach -- an approach that has been heavily influenced by Kuhn. Therefore the work of Merton (:1957), Barber (:1962a), and such exponents as Storer (:1966), Gaston (:1970), Zuckerman (1967), Cole and Cole (:1967; :1968), and Cole (:1970) will not be considered in detail, but the general position adopted by this school will be briefly sketched.

In the following section, the work of Kuhn (:1962; 1970a; :1970b) will be discussed in some detail. Then the work of the sociologists who have been strongly influenced by Kuhn, will be covered. Among these authors will be Barnes and Dolby (:1970) and Mulkay (:1969; :1970a; :1970b; and Williams :1971; and Turner :1971) who have most clearly indicated certain basic incompatibilities between

the positions of Kuhn and Merton. The work of Mullins (:1966; :1968; :1968a; :1971) who originally worked mainly within the American network tracing school, but who has recently moved to a position that is very strongly influenced by Kuhn, will also be examined. Fisher's (:1966; :1967) facinating work on the importance of disciplinary labels will then be discussed. The work of Ben David, and his collaborators will be mentioned. Hagstrom's book, (:1965) although falling ostensibly within the functionalist school, will also be review and the work of Ben David will be briefly reviewed.

This review outlines some important issues in contemporary sociology of science and illustrates some approaches that seem to the author to be the most fruitful.. A number of positions that the author believes to be mistaken will of necessity be mentioned, but the main purpose is to provide a background for the theoretical scheme developed in Chapter Eleven.

10.2 The Mertonian School in the Sociology of Science

Until recently the Mertonian school has been the most influential and indeed virtually the only approach to the sociology of science up until quite recently. In Social Theory and Social Structure (Merton :1957:533) Merton outlined this main interest. Firstly, he has been concerned to elucidate the relationship of interdependence that exists between science and other aspects of the social structure. He has developed an approach that treats science as a social institution, with its own distinctive norms. Secondly, Merton has attempted a functional analysis of this interdependence.

The norms that Merton proposes characterise the institution of science are as follows:

(1) Universalism. This norm enjoins the scientist to examine claims about truth in relation to certain criteria that are established and known beforehand. The criteria come from previously established knowledge, on the one hand, and from observation on the other. The implication of this norm is that it is irrelevant where knowledge comes from as the standards are, as it were, "universal".

(2) Communism. This norm, later rephrased as communality, denies that scientists have any exclusive rights over knowledge that they have discovered. In practical terms, it enjoins them to publish.

(3) Disinterestedness. This is a norm that Merton does not specify very closely, but it appears to relate to the proposition that the scientist should not seek, directly, any reward for the work that he carries out.

(4) Organised scepticism. The notion that judgement should be withheld until the facts are at hand, and then the examination of the truth claim in terms of existing empirical and logical criteria.

At various times these norms have been supplemented, but without essential revision. Barber (:1962a) mentions rationality, which he sees as "devotion to the 'truth' which the rational conceptual schemes of science can discover" (Barber :1962a:125). Scepticism is transformed into "emotional neutrality", and Barber also mentions individualism. Autonomy is another norm that Merton enjoins (if the scientific institutions lose their autonomy, then there is danger that the other norms will be undermined). Barber calls this "individualism" or anti-authoritarianism.

In this view, science is seen as an exchange system. The scientist offers knowledge to the scientific community (obeying, in this respect, the norm of communality). He does this, not for personal gain of a

direct sort, but, if the knowledge is found to be up to the standards of the community (and here the norms of universalism, organised scepticism and rationality are seen as operating), then it will be accepted (that is to say, published and cited) and through this acceptance the scientist receives prestige, and deference from his colleagues. Many sociological contributions have illustrated and extended this insight. Papers about the distribution of prestige, the name ordering of scientists, the "Matthew Effect" and so on, can be seen in this tradition. Priority disputes, and the degree of deviance from the norms, are matters of interest for the Mertonian. In this way, a writer like Gaston is able to propose that British science is closer to the norm of universalism than some areas of American science (Gaston :1970).

The second aspect of Merton's concern is also relevant here. The norms of science, as proposed above, are seen, on the whole, as being functional for the growth of science and deviance is seen as being disfunctional. In addition it was proposed, especially in the thirties and forties that there was a basic consonance between the norms of science as identified, and general norms and values in liberal societies. Thus, it was proposed that science would advance less effectively in Nazi Germany (Merton :1957:537) and in Soviet Russia (Barber :1962a:122), since the values of these societies were inimical to the values of science. Barnes and Dolby (:1970) note that these arguments were largely dropped after 1957. Concern with the relationship between the rise of science and ascetic protestantism is another aspect of the interest in the relationships between science and society. Some of Merton's earliest work was on this theme (Merton :1957:574; 1957:607).

This tradition has produced much important work, and it is only recently that it has come under sustained criticism from other sociologists. Briefly, Merton proposes that the institution of science is distinguished by a number (four or six) of norms which relate to the creation and handling of knowledge. While these norms are operative, scientific knowledge accumulates. In so far as the norms are not obeyed, science develops less satisfactorily than it might. Scientists are motivated by desire for recognition (or in the case of Storer, by desire for "competent response"), and in order to gain recognition they produce knowledge. The relationships between the values of science, and those of society are studied. The tradition has also produced work on industrial scientists (e.g. Kornhauser :1963; Marcson :1960) with the suggestion that the industrial scientist finds himself in a position of potential value conflict with, on the one hand, the values of the organisation, and on the other the norms and values of science.

The most general line of criticism that has been recently developed (aside from reservations about the status of functionalist explanation) depends on contrasting the norms sketched out above with that system of social control that rests in the knowledge -- the theories, methods, instruments and so on. The latter is implicit in Kuhn's work. One of the most distinctive features of the Mertonian approach is the way it avoids discussing the actual content of science. The norms are general ones, concerning the "rules of knowledge handling game's". This line of criticism has been mounted by Barnes and Dolby (:1970) and Mulkay (:1969). Other reservations have also been voiced, however. Firstly, it has been suggested that the norms of science are perhaps, not in themselves, distinctively scientific -- that they may

characterise the academic community rather than scientists. Secondly, it has been suggested that so widespread are the deviations from these norms, that it would be better to develop a scheme which systematically organised these deviations, instead of looking on them as manifestations of pathology to be explained on a one-off basis. Thirdly, doubts have been expressed about the continuity of values from seventeenth century British science to the present day. Fourthly, doubt has been cast on the proposition that scientists in industry are really in a state of conflict.

10.3 Kuhn

Kuhn's work will now be introduced, and its sociological and philosophical implications will be discussed.

10.31 Outlines of Kuhn's Approach in 1962

Kuhn's basic view can be described quite simply. He is concerned with describing and understanding the development of science. Unlike positivist philosophers of science, and many scientists, he does not look upon scientific development as being, in any easy sense, cumulative. Conceptual frameworks, which he calls paradigms, are established in scientific disciplines, and these guide research effort for a time, perhaps many hundreds of years. During that time the practitioners in that discipline view the world through conceptual blinkers -- they see only certain sorts of phenomena, and they relate them together in particular sorts of ways. The given paradigm is not the only way of looking at the world -- it does not have prior epistemological status -- but depends on (a) its ability to solve problems that in the course of events it is confronted with, and (b) its ability to

command the support of the relevant group of scientists. Thus, the paradigm is dependent on a special sort of social consensus.

The most effective way in which this consensus is maintained is through a strong socialisation procedure. The apprenticed scientist is taught dogmatically that a particular conceptual frame-work and set of procedures is the correct, and the only correct way of viewing the world. This view of the world is also sustained by a reconstructed history of the relevant discipline, in which scientific change is viewed as being cumulative. Past errors are seen as having been the result of stubbornness and prejudice. Consensus is maintained, because if a contribution to knowledge is to be treated as valid it must lie within the boundaries set for acceptable solution by the paradigm.¹

Paradigms have two important features. Firstly, they attract adherents (as mentioned above) and secondly they are open ended. That is to say, although any given paradigm has solved some scientific problems, it also has the promise of being able to solve more. In practice, a paradigm includes:

... some accepted examples of actual scientific practice -- examples which include law, theory, application, and instrumentation together -- provide models from which spring particular coherent traditions of scientific research.
(Kuhn :1970a:10)

The fact that a paradigm is a group commitment means that the scientist can work without continually restating his basic assumptions. By virtue of these assumptions scientists can concentrate all their effort in particular areas which because of the nature of the paradigm are held to be particularly important.

1. Kuhn does not, as far as I can tell, make this point explicitly, but it is implicit in what he says. He says, for example, that a scientist who fails to solve a puzzle is seen to have failed as a scientist.

Paradigm-bound science, which Kuhn calls "normal science" is extended by a process called "articulation". Normal science is, then, an articulation:

achieved by extending the knowledge of those facts that the paradigm displays as particularly revealing, by increasing the extent of the match between those facts and the paradigm's predictions, and by further articulation of the paradigm itself. (Kuhn :1970a:24)

Since the paradigm provides a set of conceptual blinkers, the scientist does not normally develop fundamental innovations. In the area of fact gathering, the permitted activities are:

- (1) Elucidating that class of facts that the paradigm has shown to be especially revealing -- this type of fact increases the accuracy and scope of the paradigm.
- (2) Facts, which although not intrinsically interesting, can be compared with prediction of the paradigm.
- (3) Empirical work to articulate the paradigm, including the attempt to resolve residual ambiguities, the determination of physical constants, the development of quantitative laws, and the extension of paradigms to new areas.

In the area of theoretical development, the permitted activities are:

- (1) The use of existing theory to predict facts of intrinsic interest.
- (2) The matching of fact and theory, and,
- (3) The development and reformulation of paradigm theory.

Kuhn does not see a clear distinction between fact and theory. Facts are selected by the paradigm, they are not the given, but the "taken with difficulty". Furthermore, the paradigm provides a cognitive framework which interprets the sense data, so that in a real sense, what a Copernican saw when he looked at the planets, is not what we see when we look at the planets. Observation is bound to theory in complex

and insoluble ways.

How does the paradigm limit the possible solutions? It does so partly directly and partly through a set of rules about acceptable work.

The types of rules which may emerge from paradigms include:

- (1) Explicit statements of scientific law, concepts, and theories.
- (2) Commitments to certain sorts of instrumentation, and certain preferred ways of using those instruments.
- (3) A set of quasi methodological commitments, which refer, for example, to the types of entities that will appear in the theory, and with which the universe is populated.
- (4) A general concern to understand the world, and assumptions about the regularity of nature.

It is not always easy to obtain agreement about what constitute the rules in a scientific tradition. Kuhn suggests that there may be no uniform rules, but rather, as in Wittgenstein's term, there may be "family resemblances" -- that is networks of overlapping and criss-crossing resemblances. Kuhn writes that:

What (research problems and techniques in a normal science tradition) have in common is not that they satisfy some explicit or even some fully discoverable set of rules and assumptions that gives the tradition its character and its hold upon the scientific mind. Instead, they may relate by resemblance and by modeling to one or another part of the scientific corpus which the community in question already recognizes as among its established achievements. Scientists work from models acquired through education and through subsequent exposure to the literature often without quite knowing or needing to know what characteristics have given these models the status of community paradigms. And because they do so, they need no full set of rules. The coherence displayed by the research tradition in which they participate may not imply even the existence of an underlying body of rules and assumptions that additional historical or philosophical investigation might uncover. That scientists do not usually ask or debate what makes a particular problem or solution legitimate tempts us to suppose that, at least intuitively, they know the answer.

But it may only indicate that neither the question nor the answer is felt to be relevant to their research. Paradigms may be prior to, more binding, and more complete than any set of rules for research that could be unequivocally abstracted from them. (Kuhn :1970a:45-46)

Kuhn advances four reasons for this position which are as follows:

- (1) The difficulty of determining rules of scientific conduct, even though scientists may agree about the identification of a shared paradigm.
- (2) Scientists never learn laws, theories and concepts in the abstract; they are always learned in conjunction with applications; scientific training involves the study of these concrete examples.
- (3) Normal science can proceed without rules when it is successful. It is only when it runs into major problems and enters a time of crisis that rules are articulated.
- (4) Finally, science is undoubtedly a ramshackle structure; some of its problems are large, and others are small. Kuhn suggests that the diversity of fields is best explained by the existence of paradigms. Some paradigms may be very local. The laws of quantum mechanics, for example, mean very different things to different kinds of scientists, and this is because the laws are worked out in relation to different examples -- and these are different paradigms.

Although scientific research is guided by the paradigms most of the time, from time to time a problem crops up which defies solution within the existing conceptual framework. Although there are many unsolved puzzles, only occasionally does one come to be seen as very important. Then it becomes, in Kuhn's terms, an anomaly. An anomaly frequently provokes a crisis, both conceptually and professionally. Conceptually, because it will not fit into the existing conceptual framework. Socially, because if practitioners are aware of this state of affairs, then they are liable to feel insecure.

When an anomaly arises scientists do not abandon their existing paradigm. (They only abandon one paradigm in favour of another, since without a paradigm they cannot really be said to be scientists at all.) Instead they concentrate on the anomaly, and try to develop an understanding of its structure. The rules of normal science are loosened because many scientists, in trying to solve the anomaly, develop articulations of existing theory which are contrary to one another, and only partially satisfactory. All crises start with a blurring of the rules and they end in one of the following three ways:

- (a) A normal science solution is found and the paradigm re-asserts itself.
- (b) No solution is developed, and the problem is set aside.
- (c) A new candidate for a paradigm emerges.

The third is not, in Kuhn's view, the result of a process of accumulation. It is rather, a more or less radical reconstruction, which is similar to a gestalt switch. It involves a fundamentally different way of viewing the world, and for this reason, a new paradigm is frequently put forward by either a young worker (whose mental sets have not become rigid, and tied to the old way of thinking) or by a worker who has transferred from a different field. The problems of the old and new paradigms may overlap, but this does not necessarily happen. Since a whole way of looking at the world is overthrown, and since for Kuhn there can be no such thing as a neutral observation language, it follows that even the concepts and empirical entities considered may change with a paradigm change. The reception of a new paradigm may thus involve complete redefinition of a field of science. Some problems which were formerly scientific may be declared unscientific while old anomalies may achieve the status of tautologies.

The relationship between the two paradigms is such that not only are they incompatible, but they are also incommensurable.¹ It follows that two schools with different paradigms cannot engage in scientific dialogue as we normally understand the term. In an important sense, they tend to talk through one another.

For Kuhn, then, science develops through scientific revolutions, followed by the establishment of paradigms, and a period of normal science, when the existing paradigms are being articulated. Then an anomaly occurs, and there may be a further scientific revolution, and a new paradigm is established. Science, in a primitive state, is at what he calls a "pre paradigm" stage -- when there is no universally acknowledged paradigm, but there are a number of schools, which talk through one another. Science, in its modern sense, starts when one paradigm achieves an ascendancy over all others.

The process of paradigm change is not along "rational" lines, since there is no guiding set of rules and no bridging scientific methodology that determines which is the superior paradigm. The most effective arguments in converting scientists from an old paradigm to a new one have been:

1. The claim that the new paradigm can solve, or alternatively make redundant, the anomaly that has been the source of crisis in the old paradigm. In addition, an indication of quantitative superiority has often been important. However, these, in themselves, have often not been sufficient.
2. The establishment of unexpected discoveries from another

1. Literally interpreted, it is difficult to understand how paradigms could be both incompatible and incommensurable at the same time, although it is clear enough what Kuhn means.

area, which corroborate the new theoretical framework.

3. Aesthetic arguments. These apply particularly to the more mathematical areas of science.

4. Arguments that the paradigm holds out great future promise.

If a paradigm is to flourish it must first find some supporters who will develop it in its initial stages up to a point where it becomes sufficiently attractive to gain wider support. Many scientists, and particularly those whose mental sets are well formed and rigid, may not be willing to transfer allegiance to the new paradigm. However, if the latter is visibly successful, then they may find it difficult to perpetuate themselves, and the adherents to the old paradigm will die leaving no followers. Science is thus potentially very fluid even though individual scientists may be resistant to change.

Kuhn's main concerns are as follows, therefore:

1. The development of scientific knowledge.
2. Rejection of the notion that certain procedures, that is "the scientific method" as such, will lead to the establishment of increasing truth, or even a near approximation to it.
3. To show that the reason why knowledge appears to be cumulative lies in the nature of scientific culture and social structure. Scientists adhere to a large body of presuppositions and established exemplars.
4. What constitutes good or bad science, or acceptable or unacceptable methodology at any time must be seen in relation to those exemplars.
5. Scientific action cannot be fully described in terms of

rules.

6. Science advances through alternate revolution and cumulation.

7. There is no independent observation language.

Kuhn's views are obviously at variance with important schools of thought both within the philosophy and sociology of science. Thus, his view of the philosophy of science is incompatible with a positivist analysis of the philosophy of science, since he sees no clear distinction between the context of discovery and the context of justification. He writes:

.. many of my generalizations are about the sociology or social psychology of scientists; yet at least a few of my conclusions belong traditionally to logic or epistemology. In the preceding paragraph I may even seem to have violated the very influential contemporary distinction between "the context of discovery" and "the context of justification". ...

Having been weaned intellectually on these distinctions and others like them, I could scarcely be more aware of their import and force. For many years I took them to be about the nature of knowledge, and I still suppose that, appropriately recast, they have something important to tell us. Yet my attempts to apply them, even grosso modo, to the actual situations in which knowledge is gained, accepted and assimilated have made them seem extraordinarily problematic. (Kuhn :1970a:8)

Such situations must, he suggests, grow out of the knowledge, and the way in which they operate varies from field to field. This view is obviously unacceptable to the positivist, who relegates sociological and psychological factors to the "context of discovery", and reserves for purely logical examination, "the context of justification".

10.32 Kuhn and Popper

Kuhn's work bears a strange relationship to that of Popper and his followers. Some observers have felt that the work of Lakatos (:1970) for example, is in some respects very similar to that of Kuhn, yet Kuhn seems more willing to acknowledge the similarity

than Lakatos. This debate has been publically developed in Criticism and the Growth of Knowledge (Lakatos and Musgrave :1970).

Kuhn writes:

On almost all occasions when we turn explicitly to the same problems, Sir Karl's view of science and my own are nearly identical. We are both concerned with the dynamic processes by which scientific knowledge is acquired rather than with the logical structure of the products of scientific research. Given that concern, both of us emphasize, as legitimate data, the facts and also the spirit of actual scientific life, and both of us turn often to history to find them. From this pool of shared data, we draw many of the same conclusions.

(Kuhn :1970b:1)

He lists some of these conclusions: the emphasis on change and overthrow in science, rather than on accretion; the manner of the overthrow of old theory; the entanglement between theory and observation. Then he writes:

That list, though it by no means exhausts the issues about which Sir Karl and I agree, is already extensive enough to place us in the same minority among contemporary philosophers of science. Presumably that is why Sir Karl's followers have with some regularity provided my most sympathetic philosophical audience, one for which I continue to be grateful. But my gratitude is not unmixed. The same agreement that evokes the sympathy of this group too often misdirects its interest.

(Kuhn :1970b:2)

Thus Kuhn suggests that the Popperians tend to become involved in side issues, and it is non-Popperians who usually recognise his central concerns (although often without sympathy). He suggests that although he and Popper have much in common, their intentions are often different when they talk about the same phenomena, or use the same language. He describes the difference between himself and Popper as a gestalt switch -- there is great similarity, but what emerges is in many respects quite different.

The first apparent similarity is the agreement between himself and Popper that in the philosophy of science, it is necessary to look at the way in which science has actually developed. The leads

both of them to recognise that there are revolutionary episodes in science, when entire conceptual frameworks are overthrown. Kuhn quotes Popper as saying:

A scientist, whether theorist or experimenter, puts forward statements, or systems of statements, and tests them step by step. In the field of the empirical sciences, more particularly, he constructs hypotheses, or systems of theories, and tests them against experience by observation and experiment.

(Popper, from Kuhn :1970b:4)

For Kuhn this does not make sense, because ~~the only~~ sort of normal testing in science is that in which the individual scientist tests his guesses about the best way to connect his own research with the body of normal science. Even at times of scientific revolution he never tests general theories or hypotheses in the manner that Popper proposes. Kuhn writes:

I suggest that Sir Karl has characterized the entire scientific enterprise in terms that apply only to its occasional revolutionary parts. His emphasis is natural and common: the exploits of a Copernicus or Einstein make better reading than those of a Brahe or Lorentz; ... (Kuhn :1970b:6)

The second area of agreement concerns Popper's use of the term "mistake". For Kuhn a mistake is a personal attribute or action. An individual can make mistakes. He notes about Popper that:

The mistakes to which he points are not usually acts at all but rather out-of-date scientific theories: Ptolemaic astronomy, the phlogiston theory, or Newtonian dynamics, and 'learning from our mistakes' is, correspondingly, what occurs when a scientific community rejects one of these theories and replaces it with another.

(Kuhn :1970b:11)

This does not make sense to Kuhn. What kind of a mistake was it to be a Ptolemaic astronomer at a time when all other astronomers also believed in the same system? The most that can be argued is that either a theory which was not previously a mistake has become

one, or that a scientist can make the mistake of hanging onto a theory for too long. The term "mistake" cannot be applied to revolutionary episodes. It is only within normal science, and as applied to the actions of individuals, that it makes sense to talk about mistakes.

The third difference concerns Popper's criterion of demarcation -- that a statement, to be scientific, must be falsifiable. Kuhn does not believe that any prior demarcation criterion of this sort can, in practice, be made to work. There are a number of difficulties in the view held by Popper. First, unless one is a naive falsificationist and believes in a neutral observation language, then it is unclear what constitutes a refutation of a scientific theory. Secondly, Kuhn believes that it is probably in principle, impossible to decide in advance in all cases what would constitute a falsification. This is because of the nature of the paradigm, which is not a set of well defined theories, but is rather a set of exemplars which illustrate laws, generalisations, and so on. A proposed extension of theory or a new discovery may constitute neither a confirming nor a falsifying instance. This is clearer if one thinks of a paradigm as a metaphor, since it may be possible to extend the metaphor in unexpected ways, and still maintain the integrity of the model as a whole. Kuhn writes:

The books and teachers from whom (scientific knowledge) is acquired present concrete examples together with a multitude of empirical generalizations. Both are essential carriers of knowledge, and it is therefore Pickwickian to seek a methodological criterion that supposes the scientist can specify in advance whether each imaginable instance fits or would falsify his theory. The criteria at his disposal, explicit and implicit, are sufficient to answer that question only for the cases that clearly do fit or that are clearly irrelevant. These are the cases he expects, the ones for which his knowledge

was designed. Confronted with the unexpected, he must always do more research in order further to articulate his theory in the area that has just become problematic. He may then reject it in favour of another and for good reason. But no exclusively logical criteria can entirely dictate the conclusion he must draw. (Kuhn :1970b:19)

Finally, Kuhn draws attention to the problem of scientific progress.

There is no clear answer to this problem, but he notes:

Already it should be clear that the explanation must, in the final analysis, be psychological or sociological. It must, that is, be a description of a value system, an ideology, together with an analysis of the institutions through which that system is transmitted and enforced. (Kuhn :1970b:21)

The form that an answer will take is not clear to Kuhn. He suggests, rather tentatively, that if a scientist is trained as a puzzle solver, then he will wish to retain as much as possible of the prior puzzle solutions obtained by his group, but "he will also wish to maximize the number of puzzles that can be solved". These two values may conflict, and it is possible that maintenance of group unity may, at times, be of the greatest importance.

For a long time Kuhn assumed that Popper would be unable to agree with this view, as the latter had constantly rejected the "psychology of knowledge" in favour of study of the logic of knowledge. In fact, however, there may be a trace of the sociological or social psychological view espoused by Kuhn. Kuhn agrees that the source of the individual's inspiration is not a relevant object of study in this context, while noting that Popper on occasion implies a certain group imperative. Kuhn concludes:

We shall not, I suggest, understand the success of science without understanding the full force of rhetorically induced and professionally shared imperatives like these. Institutionalized and articulated further (and also somewhat differently) such maxims and values may explain the outcome of choices that could not have been dictated by logic and experiment alone.

(Kuhn :1970b:22)

10.33 Kuhn :1969

The term "paradigm" has caused some of the main difficulties in Kuhn's work, perhaps because of two main reasons. Firstly, it is an idea that is unfamiliar. Secondly, in the text of The Structure of Scientific Revolutions the term is used loosely and ambiguously.

Kuhn writes:

The term 'paradigm' enters the preceding pages early, and its manner of entry is intrinsically circular. A paradigm is what the members of a scientific community share, and, conversely, a scientific community consists of men who share a paradigm. (Kuhn :1970a:176)

This circularity can easily be avoided if scientific communities are first isolated without considering paradigms. Once the communities have been discovered, then the shared paradigms can be identified. Hagstrom, Price, Mullins and Crane have all worked on the identification of the community structure of science.

A community consists of a group of scientists who have undergone the same socialisation procedure, and absorbed the same technical literature. The scientists in a community normally see themselves as pursuing shared goals by means of shared standards; in addition the group of scientists maintains a high rate of internal inter-communication. Communication between communities is much less frequent, because the different communities pursue different goals.

It is true, of course, that communities exist at varying levels. The most global community is that of "scientists". Below that there are professional groups, chemists, physicists, and so on. Then there are specialties -- organic chemistry, for example. Identification of the community at any of these levels is relatively easy. Postgraduate degrees, professional society membership,

journal of publication, and so on, act as suitable indicators. He continues that:

It is only at the next lower level that empirical problems emerge. How, to take a contemporary example, would one have isolated the phage group prior to its public acclaim?
(Kuhn :1970a:177)

Here he suggests attendances at special conferences, preprint and reprint distribution, and the discovery of informal communication networks. These procedures will yield communities "of perhaps one hundred members, occasionally significantly fewer". Individual scientists belong to more than one such community. Kuhn writes:

Communities of this sort are the units that this book has presented as the producers and validators of scientific knowledge. Paradigms are something shared by the members of such groups. (Kuhn :1970a:178)

There are a number of outstanding problems that can be cleared up with reference to the group structure of science. Firstly, he now argues that the development of a mature science, which he previously characterised as the acquisition by a group of a paradigm, should instead be seen as a change in the nature of a pre-existing paradigm such that a puzzle solving tradition becomes possible. Secondly, there is the implicit assumption in the book that there is a one-to-one identification between paradigms and subject matters, which is now abandoned. If the community structure of science is studied, then it is clear that different paradigms may be concerned with different aspects of the same subject matter. The paradigm does not govern a subject matter -- it governs a group of practitioners. Thirdly, looked at in this way, revolutions need not be global in their implications. He writes:

A revolution is for me a special sort of change involving a certain sort of reconstruction of group commitments. But it need not be a large change, nor need it seem revolutionary to

those outside a single community, consisting perhaps of fewer than twenty-five people. (Kuhn :1970a:180)

In the next section Kuhn introduces two new terms which he proposes to use instead of "paradigm". These terms are "disciplinary matrix", and "exemplar". "Disciplinary matrix" represents the largest part of the element of group commitment that had previously been entailed in the term "paradigm". The shared commitments are called "disciplinary matrix":

'disciplinary' because it refers to the common possession of the practitioners of a particular discipline; 'matrix' because it is composed of ordered elements of various sorts, each requiring further specification. (Kuhn :1970a:182)

Kuhn mentions four components of the disciplinary matrix:

1. "Symbolic generalisations" are:

deployed without question or dissent by group members, which can readily be cast in logical form They are the formal or the readily formalizable components of the disciplinary matrix. Sometimes they are found already in symbolic form: $f = ma$ or $I = V/R$. Others are ordinarily expressed in words: "elements combine in constant proportions by weight", or "action equals reaction". (Kuhn :1970a:183)

The community can attach mathematical techniques of manipulating to symbolic generalisations in order to solve puzzles. The generalisations are not just laws of nature, but also define the symbols which constitute them. The balance between their legislative and definitional functions varies over time.

2. There are commitments to what were previously described a "metaphysical beliefs" -- beliefs in entities such as matter and force, fields, and the fact that kinetic energy of the constituent parts of bodies is heat:

Rewriting the book now I would describe such commitments as beliefs in particular models, and I would expand the category models to include also the relatively heuristic variety: the electric circuit may be regarded as a steady-state hydrodynamic system; the molecules of a gas behave

like tiny elastic billiard balls in random motion. Though the strength of group commitment varies, with nontrivial consequences, along the spectrum from heuristic to ontological models, all models have similar functions. Among other things they supply the group with preferred or permissible analogies and metaphors. By doing so they help to determine what will be accepted as an explanation and as a puzzle-solution; conversely, they assist in the determination of the roster of unsolved puzzles and in the evaluation of the importance of each. (Kuhn :1970a:184)

3. Values. These are more general and widely shared, and help to give a feeling of community to scientists as a whole. While they exist at all times, they become particularly important when a community is in crisis or must choose between two different paradigms. Some values concern predictions -- they should be accurate, preferably quantitative. Others are used in judging between theories. Theories should permit puzzle solving, they should be simple, self consistent, and so on.

Although values may be held in common by wide groups of scientists, the manner in which they are employed varies greatly between individuals and groups. Values may contradict one another, and cannot be unambiguously translated into action in most instances.

Some of Kuhn's critics have suggested that this sort of locution -- the insistence that shared values do not lead to uniform behaviour -- leads to a position where irrationality or subjectivity are glorified. Kuhn rejects this charge on two counts. Firstly, even though shared values are not all applied in the same way, they still act as partial determinants of group behaviour. Secondly, variability may, in itself, be functional for science. Kuhn writes:

The points at which values must be applied are invariably also those at which risks must be taken. Most anomalies are resolved by normal means; most proposals for new theories do prove to be wrong. If all members of a community responded to each anomaly as a source of crisis or embraced each new theory advanced by a colleague, science would cease. If, on the other hand, no one reacted to anomalies or to brand-new theories in high-risk ways, there would be few or no revolutions. (Kuhn :1970a:186)

4. The fourth element of the disciplinary matrix is what Kuhn now wishes to call "exemplar".

By it I mean, initially, the concrete problem-solutions that students encounter from the start of their scientific education, whether in laboratories, on examinations, or at the ends of chapters in science texts. To these shared examples should, however, be added at least some of the technical problem-solutions found in the periodical literature that scientists encounter during their post-educational research careers and that also show them by example how their job is to be done. More than other sorts of components of the disciplinary matrix, differences between sets of exemplars provide the community fine-structure of science. (Kuhn :1970a:187)

The cognitive content of science, in Kuhn's view, is located in the examples and not in a set of scientific laws. Newton's Second Law of Motion is generally written as $\underline{f} = \underline{ma}$, but:

The sociologist ... or the linguist who discovers that the corresponding expression is unproblematically uttered and received by the members of a given community will not, without much additional investigation, have learned a great deal about what either the expression or the terms in it means, about how the scientists of the community attach the expression to nature. Indeed, the fact that they accept it without question and use it as a point at which to introduce logical and mathematical manipulation does not of itself imply that they all agree at all about such matters as meaning and application. (Kuhn :1970a:188)

It is necessary to learn to pick out the appropriate forces, masses, and accelerations in any given problem situation. However, the situation is more complicated than this. Logical and mathematical manipulation are not applied to "law sketches" such as $\underline{f} = \underline{ma}$ directly. The symbolic generalisations to which manipulation is applied vary from one situation to the next and the "law sketch" takes different forms. How does the student learn to identify the relevant variables and how does he learn to apply the best version of the law-sketch?

Part of the answer to this can be gained by looking at the process of socialisation of the student. The student studies his text book, and tries to apply his knowledge to the problems that are typically

set at the end of each chapter. In the initial stages of training the student often fails. He has to develop an ability to see analogies between what he has already learned, and the problem with which he is confronted. Kuhn writes:

Having seen the resemblance, grasped the analogy between two or more distinct problems, he can interrelate symbols and attach them to nature in the ways that have proved effective before. The law-sketch, say $f = ma$, has functioned as a tool, informing the student what similarities to look for, signaling the gestalt in which the situation is to be seen. The resultant ability to see a variety of situations as like each other, as subject for $f = ma$ or some other symbolic generalization, is, I think, the main thing a student acquires by doing exemplary problems, whether with a pencil and paper or in a well designed laboratory. (Kuhn :1970a:189)

Kuhn describes this situation as that of "acquired similarity relations". New puzzles are solved by approaches modeled on previous puzzle solutions, and symbolic generalisations may be quite secondary to this process. Learning is not an exclusively verbal process, but is rather a combination of rules and application.

The fact that knowledge is contained in exemplars does not mean that it is unsystematic. He writes:

I have in mind a manner of knowing which is misconstrued if reconstructed in terms of rules that are first abstracted from exemplars and thereafter function in their stead. (Kuhn :1970a:192)

In order to develop this point he digresses to discuss the relationship between the reception of a stimulus and the awareness of a sensation. The same stimulus can produce different sensations, and different stimuli can produce the same sensation. He notes that "the route from stimulus to sensation is in part conditioned by education". While we may all, under the same conditions, receive the same stimuli, we do not necessarily experience the same sensation. In some sense then, people in this situation do not live in the same world. None the less, where people live in groups and share education, language and

culture, it is reasonable to suppose that the sensations experienced are the same. But if there is differentiation or specialisation of groups this no longer holds true.

Kuhn continues:

Returning now to exemplars and rules, what I have been trying to suggest, in however preliminary a fashion, is this. One of the fundamental techniques by which members of a group, whether an entire culture or a specialists' sub-community within it, learn to see the same things when confronted with the same stimuli is by being shown examples of situations that their predecessors in the group have already learned to see as like each other and as different from other sorts of situations. (Kuhn :1970a:193)

It is reasonable to suggest that this is a process like learning a rule? Although there is a strong temptation to describe it in this way, it is not in fact correct. The recognition of similarity may be an involuntary process. One may only talk about a rule if it is voluntary and might be disobeyed because there are other accessible alternatives. It is only possible to deliberate between two alternatives once the actor has had a sensation, that is, he has perceived something. Interpretation is then possible, but this is not the same as what is involved in perception. The fact that interpretation can be seen as rule-bound in no way implies the same for perception.

Making this distinction Kuhn talks about the "knowledge" that is "embedded in the stimulus-to-sensation route". Knowledge might not be the best word, but he goes on to elaborate what he means in the following way:

What is built into the neural process that transforms stimuli to sensations has the following characteristics: it has been transmitted through education; it has, by trial, been found more effective than its historical competitors in a group's current environment; and, finally, it is subject to change both through further education and through the discovery of misfits with the environment. Those are characteristics of knowledge, and they explain why I use the term. But it is strange usage, for one other characteristic is missing.

We have no direct access to what it is we know, no rules or generalization with which to express this knowledge. Rules which could supply that access would refer to stimuli not sensations, and stimuli we can know only through elaborate theory. In its absence, the knowledge embedded in the stimulus-to-sensation route remains tacit. (Kuhn :1970a:196)

Kuhn next considers the nature of dialogue between holders of two rival paradigms. While it has long been held in the philosophy of science that if two opponents in a debate can show that their prior agreement does not provide an adequate basis for an agreement on what is correct, then the debate between the opponents must be about premises. This does not mean, however, that there are no good reasons for moving from one view to another. The criteria may even, to a fair extent, be the same -- accuracy, simplicity, and so on. Rather:

such reasons function as values and ... they can thus be differently applied, individually and collectively, by men who concur in honoring them. If two men disagree, for example, about the relative fruitfulness of their theories, or if they agree about that but disagree about the relative importance of fruitfulness and, say, scope in reaching a choice, neither can be convicted of a mistake. Nor is either being unscientific. There is no neutral algorithm for theory-choice, no systematic decision procedure which, properly applied, must lead each individual in the group to the same decision. In this sense it is the community of specialists rather than its individual members that makes the effective decision. (Kuhn:1970a:199)

The situation is partly one of individual persuasion, rather than the tracing of logical moves. Normal science demands the ability to group objects into similarity sets which do not have a hard and fast definition as to what it is in respect to which they are similar; scientific revolutions alter some of those similarity relationships. Disparate objects come together into new similarity sets, while previously homogeneous sets of objects become broken down. There is typically a high degree of continuity between pre-revolutionary and post-revolutionary similarity sets, which enables terms employed to remain the same.

However, when the sets are redefined, scientists tend to find themselves reacting in different ways to the proposed redefinition. Since the names of the sets derive in part from exemplars, and contain a tacit element, it is impossible to define them linguistically, in a neutral way. Kuhn notes that "part of the difference is prior to the application of the languages in which it is nevertheless reflected". Since the stimuli that impinge on the disagreeing scientists are the same, their neural apparatus is the same, and they hold much of their programming in common, the scientists have a great deal in common. Under such circumstances, it is possible to explore much about their disagreement.

Briefly put, what the participants in a communication breakdown can do is recognize each other as members of different language communities and then become translators. Taking the differences between their own intra- and inter-group discourse as itself a subject for study, they can first attempt to discover the terms and locutions that, used unproblematically within each community, are nevertheless foci of trouble for inter-group discussions.... they can next resort to their shared everyday vocabularies in an effort further to elucidate their troubles. Each may, that is, try to discover what the other would see and say when presented with a stimulus to which his own verbal response would be different. If they can sufficiently refrain from explaining anomalous behaviour as the consequence of mere error or madness, they may in time become very good predictors of each other's behavior. Each will have learned to translate the other's theory and its consequences into his own language and simultaneously to describe in his language the world to which that theory applies. (Kuhn :1970a:202)

This sort of translation enables the actor to experience the strengths and weaknesses of the rival viewpoint and it can in turn lead to persuasion and conversion. But persuasion and conversion are not the same thing. Persuasion, Kuhn sees as convincing someone that one's own view is better, and ought to be adopted. It can occur without the translation process that has

translation process that has been described above.¹

Usually, however, translation becomes necessary. Although this process does not come naturally and is threatening to the normal scientist having to face continual arguments and challenges means that "only blind stubbornness can in the end account for successful resistance". But, conversion is not the same thing as persuasion. Even if the process of translation occurs it does not mean that the individual has necessarily gone over to the other side. This happens, in all probability, without any conscious decision being made by the individual. In certain circumstances an actor may be intellectually convinced of the correctness of the new view, without ever feeling really at home in the world created by that new theory.

So, though it is possible to examine persuasion and translation, in the final resort it is conversion, a process similar to a gestalt switch, which is at the centre of the revolutionary change from paradigm to paradigm.

A number of his critics have suggested that this position is relativist, but Kuhn does not accept this, suggesting that the main criterion used at times of theory choice is likely to be the relative puzzle solving abilities of two different theories. He is in no doubt

1. This results because each group may be able to indicate that it has achieved a number of concrete puzzle solutions in language that is comprehensible to the other group. If the other group has not achieved the puzzle solutions by means of its own tradition, and if the first group goes on adding to the class of achieved puzzle solutions in a manner comprehensible to the other group, then this, by itself, will be sufficient to draw a number of adherents. People who are not deeply socialised into the rival point of view are those who are most amenable to this sort of persuasion.

that there are differences between early theories and those that appeared at a more developed point. Among the possible criteria for distinguishing between theories he mentions: accuracy of prediction (especially quantitative prediction); balance between everyday and esoteric subject matter; number of problems solved. He writes:

Those lists are not yet the ones required, but I have no doubt that they can be completed. If they can, then scientific development is, like biological, a unidirectional and irreversible process. Later scientific theories are better than earlier ones for solving puzzles in the often quite different environments to which they are applied. That is not a relativist's position, and it displays the sense in which I am a convinced believer in scientific progress. (Kuhn :1970a:206)

One normally accepted aspect of progress is missing from the above formulation -- the notion that the newer theories are closer to what nature "is really like". He sees no theoretically independent way of discovering what is "really there", and:

the notion of a match between the ontology of a theory and its "real" counterpart in nature now seems to me illusive in principle. (Kuhn :1970a:206)

Finally, he raises two further points. The first concerns the distinction between the descriptive and normative modes. Kuhn sees no clear distinction between the two. Since he offers an account through which he hopes science and scientific change may be understood, it follows that it is legitimate to make normative statements. If he slips from time to time into the normative mode this does not worry him. He is happy to see the theory developing, and being applicable to increasing areas of the history of science.

The second point that he raises is whether any of the main theses of the book are applicable to areas other than science. Notions of revolution and normal science may be applicable to other areas of cultural endeavour and the exemplar may be of use in the arts. On the

other hand, the sciences are distinct from other areas of human activity in that they progress (whatever that may mean). There are normally no competing schools in a mature science, and the main scientific activity of science is puzzle solving, which is not true of other cultural spheres. He concludes by calling for studies of the community structure, not only of science, but also of the arts. Studies of socialisation procedures, studies as to how goals are defined, studies of deviant behaviour -- all of these are required.

How does the view of science put forward in this postscript differ from the earlier view put forward in the main body of The Structure of Scientific Revolution? The answer to this question can be summarised under three headings.

1. There is a detailed reformulation of the term "paradigm" which is now replaced by that of "disciplinary matrix". This has four constituent parts. There are: 1. symbolic generalisations, 2. models, 3. values, and 4. exemplars. The cognitive content of science is seen as being located largely in the exemplars; scientists are trained by learning exemplars; and they acquire tacit similarity relationships that are not fully rule-explicable. The tacit knowledge is in the stimulus to sensation route.

It might be argued that all this is present in the Structure of Scientific Revolutions. This would not be fully correct, however. Although much of it is implicit, and some of it is explicit, it is only in the Postscript that it is worked out (all be it in sketch form) for the first time. The exemplary aspects of paradigm have been explained more carefully. The notion of a programme which is internalised by actors undergoing similar socialisation processes leading them to similar reactions in similar circumstances, which is nonetheless not rule bound has been properly defended.

2. 2. As an aspect of the above, it is now easier to talk about innovation in science, both of a normal and a revolutionary kind. Much of the time this takes the form of metaphorical extension, which is not fully bound by rules.¹

3. Finally, Kuhn is more concerned with the community structure of science, explicitly arguing that it is necessary to elucidate the group structure of science before turning to the cognitive element. While this means that he is becoming more explicitly sociological in his approach to science, this is also one of the sources of the charge that he is irrationalist, or is espousing psychologism.

In his concern with community structure Kuhn has changed his position on a couple of points. Firstly, he no longer thinks that a mature science develops as the result of the creation of a paradigm, but rather that it involves the adoption of a special sort of paradigm -- one that permits puzzle solving. Secondly, he no longer implicitly equates a single paradigm with a single subject matter. A subject matter may be the subject of inquiry of more than a single paradigm.

10.34 Summary

It should be apparent why there is tension, not to say incompatibility, between the position adopted by Kuhn, and the general position of the functionalists, who have, as has been noted, sought to understand and define the institution of science in terms of what their critics have called the "ideal norms" -- norms that concern the handling and communication of knowledge only. If Kuhn does not distinguish

1. This issue is treated in more detail in Chapter Eleven.

clearly between the context of discovery and the context of justification, then the meaning of the functionalist norm of "rationality" is no longer clear. Merton's world view is a positivist one, and both the Kuhnians and the Popperians are far from positivism.

10.4 Sociological Interpretations of Kuhn

In recent years British sociology of science has acquired a distinctive perspective which appears most clearly in the work of Mulkay and Barnes and Dolby¹. They draw attention to certain problems within the Mertonian approach and suggest that some of the problems can be avoided if the content of scientific knowledge is seen as having not only cognitive status, but also implication for action -- that it has normative status, or at least implications for social control. Both papers refer to Kuhn's work and suggest that his use of the term paradigm implies that knowledge has such a status. They hence propose that Kuhn's writing and that of Merton are incompatible.

The implications of an approach based on the normative status of scientific knowledge have yet to be worked out in detail. Mulkay is especially concerned with the nature of innovation, finding that Kuhn's account, although useful in so far as it goes, has to be supplemented by other approaches. In this section the work of these three authors is discussed in some detail.

10.41 Mulkay

Near the beginning of his paper, Mulkay writes:

The main thesis of this paper is that the most pervasive normative influence within the scientific community is provided by the body of established knowledge rather than the social norms stressed by the functionalists. (Mulkay :1969:22)

1. Mulkay :1969 and Barnes and Dolby :1970.

He describes the six Mertonian norms in some detail and shows how they are seen as contributing to the growth of knowledge. Although he finds Merton's thesis interesting, he believes that it has a number of serious defects:

In the first place, the norms which Merton suggests are peculiar to science may well be characteristic of the Western academic community in general. There have, in practice, been virtually no empirical studies to demonstrate that these norms are peculiarly characteristic of the scientific community. (Mulkey :1969:27)

Secondly, from those studies that are available, it seems that there is widespread deviance from the norms proposed by Merton. West has shown (West :1960) that those scientists who adhere to the Mertonian norms are no more productive than those who do not (although this in itself may not constitute a damning general criticism of the Mertonian approach).

Thirdly, it seems that although science has advanced, there have been instances of resistance to innovation by bodies of scientists. Mulkey argues (with reference to Taton :1962) that resistance to innovation is not a rare occurrence, but rather the rule. Yet:

Within the functionalist framework such resistance to innovations must be explained largely as minor deviations from norm of organized skepticism; they cannot be treated systematically as an integral part of the process of discovery. (Mulkey :1969:29)

He expands on this point by arguing that:

For Barber resistance to innovation is a peripheral fact which can be explained away in an ad hoc fashion. Barber's analysis would be more acceptable if there were convincing evidence of conformity to the Mertonian norms. We have seen that such evidence is not available. Through concentrating on these supposed social norms Barber fails to perceive the central importance of theory, methodological rules, etc., as elements in the normative structure of science, and how the very training which scientists undergo serves to blind them to potential new theoretical frameworks. Only by viewing theories, methodology, techniques and so on as the central normative element in the social structure of

of science can we consistently explain the pervasive resistance to innovation within science. (Mulkay :1969:29)

Fourthly, he notes that despite their concern with the accumulation of knowledge, the functionalists never actually examine knowledge in a substantial manner, and they deny any direct relationship between the structure of knowledge, and the social structure of the scientific community.¹

Mulkay goes on to discuss an example where the Mertonian norms were visibly broken by a large number of scientists -- the case of the reaction of large sections of the scientific community to the theories of Dr. Velikovsky. Although the example is an extreme one, Mulkay believes that it shows the way in which norms that are more cognitive and technical work.² He writes:

According to the functionalist approach we should have predicted that Velikovsky's work would have been subjected to detailed and critical examination by those scientists directly concerned. If any scientists had reacted publically in an emotional and negative manner they would have been restrained by reaffirmation of the Mertonian norms by their professional colleagues. As we have seen, this did not happen. Instead we find extensive deviation from the Mertonian norms in terms of actual behaviour. Furthermore, it is not the Mertonian norms which are affirmed as a means of subduing the socially deviant critics of Velikovsky; rather the established theoretical and methodological models are publically affirmed as a means of subduing the recalcitrant Velikovsky and his "supporters". All this would seem to indicate that theoretical and methodological norms are more central to the structure of the scientific community than are the Mertonian ~~normal~~ norms, at least when radical and thereby threatening innovations are involved. (Mulkay :1969:35)

1. Some of Merton's followers believe that sociological explanation has a role only in so far as there is irrationality in science. What is rational does not require a sociological explanation. That is a view similar to that of certain philosophers which has been aptly named the "dustbin" approach to the sociology of science -- sociology deals with the residue after the rational meat has been extracted. (See Cole and Cole :1970:301ff)

2. Velikovsky advanced theories that ran counter to many of the central assumptions of several disciplines -- in particular those of astronomy, geology and historical biology.

Scientific and intellectual rigidity is induced by a number of factors. Several of these have to do with the effectiveness of scientific socialisation: it lasts into adult life; it is highly demanding; it results in a narrow focus for the science student; the graduate student is highly dependent on his tutor for employment and technical guidance; scientists in a specialty learn only one consistent set of approaches to a group of problems; recruitment is highly selective.

Mulkay then uses some of Festinger's work (Festinger :1957) to suggest that the scientist, in his training, is led to a need for "cognitive consensus". Cognitive dissonance serves as a source of motivation for the actor to reduce the dissonance. A high degree of cognitive dissonance leads to a strong reaction. It would appear that the work of Velikovsky induced a high measure of cognitive dissonance amongst the relevant scientists. In order to reduce cognitive dissonance, there are three paths open to the actor.

1. He may change his existing mental set. Clearly this was extremely difficult, if not impossible, for scientists who had been through a particularly effective socialisation process;
2. He may add new cognitive elements, Mulkay suggests, that this was done by pointing out that Velikovsky was not a qualified scientist, and suggesting that he was dishonest.
3. He may change "environmental cognitive elements". Mulkay suggests that a number of scientists did this by preventing the dissemination of Velikovsky's views through the media of scientific discussion. Contrasting Merton and Kuhn's points of view, he writes that:

... Mertonian norms need not be stressed in accounting for 'normal science'. Research will be guided by the accepted paradigm and professional recognition will be gained primarily

by means of contributing to the further articulation of the paradigm within the limit provided by established technical and cognitive norms. (Mulkey :1969:41)

Since the paradigm guides scientists to particular problems, the paradigm contains within itself, the "seeds of its own destruction" -- anomalies may arise which scientists working within the specialty may not be able to solve. Mulkey now notes that:

In this sense modern science grows through the formation of closed specialties which generate new knowledge by restricting attention to a number of specific and solvable problems regarded as important within the group. However, Kuhn's scheme itself appears to have several deficiencies. In the first place, most of Kuhn's examples either deal with the emergence of specific disciplines from their pre-paradigmatic into their paradigmatic period. (Mulkey :1969:41)

He quotes Ben-David (:1964) when the latter argues that this scheme of advance is perhaps satisfactory in highly developed fields of research, where there is general agreement about what constitute central problems. In such cases, organisational inertia may be overcome. But in fields which are more diffuse, other organisational mechanisms may be required.

In addition, he points out that Holton (:1962):

has shown (that) a great deal of growth in science is due to the spread of paradigms into areas which either have not developed established paradigms of their own or which have not previously existed as distinct areas of inquiry. (Mulkey :1969:42)

The suggestion is that there are only a few interesting ideas available in any given research area. When a new area is opened up, a lot of people move into that area, and solve many of the basic problems in a relatively short period of time. Some research continues in the old lines, however. Mulkey writes that:

Science tends to proceed therefore by means of discovery of new areas of ignorance. New areas of ignorance are not associated in the minds of scientists with established paradigms. As a consequence there is far less resistance to innovation. (Mulkey :1969:42)

It seems, therefore, that he sees two processes at work in the cultural growth of science. On the one hand, there are situations such as those described by Kuhn, where there is focussed and intensive research, which finally results in innovation of a fundamental kind in a scientific revolution. This, he suggests "makes sense of the intellectual inertia" within science, and it also accounts for the rapid growth of science. In addition to such clearly defined areas, there will be sections of science where the commitments and problems are more diffuse, and change is more gradual.

On the other hand, ideas frequently escalate into new fields. Here new knowledge can be developed, without the resistance that would be expected in the tightly bound specialty. This view of the growth of science has advantages, in that it focusses the analysis on bodies of knowledge, it takes care of the normative aspects of paradigms, and it accounts for resistance to cultural change, while still allowing for rapid scientific growth.

For Mulkay, this is only a potential explanation for one half of the problem. It explains why knowledge is accepted into the scientific community but does not explain the sources of the innovation. This, he proposes, can be explained by processes of cross fertilisation -- which have been suggested by Holton and Ben-David. For Mulkay cross fertilisation is the "interplay of divergent cognitive-normative frameworks". He mentions work by Ben-David on role hybridisation (Ben-David :1960) where the latter has shown that the medical practitioners, because of the problems they faced in practice, were more willing to accept a fundamental and intellectually disreputable innovation -- a theory of bacteriology -- than were the academic medical researchers, in 19th century Germany. They were, he suggests,

more able to shift their frames of reference than were the academic researchers. Mulkey writes:

We could perhaps therefore generalize Ben-David's finding and suggest that occupancy of dual roles, insofar as these roles entail distinct approaches to similar research problems, will tend to favor the generation of new cognitive frameworks. This proposition is, of course, no more than a tentative inference. It does however appear to me to deserve further investigation. (Mulkey :1969:46)

The way in which this may happen in practice is illustrated by Barber and Fox (:1962:525) in their paper on the case of the floppy eared rabbits.¹

This paper was the first paper which contrasted the work of Kuhn with that of Merton in a systematic manner, concluding that in certain important respects the work of Kuhn was more satisfactory. Since then Mulkey has written several more papers on the sociology of natural science, and these will now be briefly reviewed. The next is an informal working paper given in 1970 (Mulkey:1970a). This paper is in two parts. In the first Mulkey asks the question -- why has Kuhn's work caused so little research in the sociology of science? His answer which is not, in my opinion, fully satisfactory, is that there are inconsistencies in Kuhn's use of crucial terms such as "paradigm" and that while these are not cleared up the sociological import of his work cannot be developed. In the second part he seeks to apply propositions derived from exchange theory to the sociology of science. Each part of this paper will be discussed in turn.

1. Here two researchers discovered separately, that when rabbits' ears were injected with crude papain, the ears collapsed. Both investigators tried to establish the reason for this, but neither of them initially succeeded. It was only when one of the investigators came to occupy the role of teacher that he suddenly saw that an easy explanation could be offered. This explanation was contrary to his expectations as researcher, but in his role as teacher he had abandoned that particular mental set and looked at the problem in a less blinkered manner

Kuhn is undoubtedly ambivalent in his use of the term "paradigm" although he has recognised this and systematised his thinking in the Postscript. It is unfortunate, therefore, that Mulkey's paper does not include a discussion of the Postscript, but deals only with the original text. Mulkey identifies two ways in which paradigms guide research. Firstly, they create mental sets which structure perception. Secondly they offer sets of ideas that are shared and prescribed in a community of scientists. Unfortunately, Kuhn sometimes uses the term loosely to describe individual perceptions and standards, and this is a first obstacle to the use of the term by sociologists.

Mulkey writes:

The focus of Kuhn's argument is the way in which particular achievements organise the thought processes of subsequent generations of scientists, thereby influencing the direction of scientific development. This aspect of the thesis, greatly indebted to gestalt psychology, is supplemented by reference to corresponding social processes, in addition to that of socialisation whereby paradigms become internalised. (Mulkey :1970a:1)

In certain respects Kuhn appears to argue that paradigms operate in the manner of cognitive norms -- they tend, for example, to lead to the suppression of conceptual novelty. Not only do they determine what constitute acceptable innovations, but they also suggest acceptable ways of bringing innovations into existence. In many important respects Kuhn's description of the role of paradigm parallels that of Sherif's description of social norms (Sherif :1966). Mulkey argues that:

It is ... possible to re-state both facets of Kuhn's concept of paradigm i.e. paradigms as group standards and paradigms as psychological frames of reference, in terms of social norms. In addition, Sherif's account of changes in social norms resembles in several respects Kuhn's description of the transition from one paradigm to another. (Mulkey :1970a:2)

He quotes Sherif who argues that norms may organise the experience of the individual and act as guides to action in a manner that is not necessarily conscious and known to the actor, at times when few

are challenging existing modes of conduct. But when they are under pressure they are more likely to be broken, and the challenge becomes effective. Transition between an old set of norms, and a new set may take place. Mulkay writes that:

(This quotation) helps me make the basic point of this first section of the paper: namely that much of Kuhn's analysis consists of examination of cognitive and methodological norms in science; and that if we conceive of paradigms as networks of cognitive norms, we should find it easier to establish links between Kuhn's work and the findings of social psychology and sociology. In particular if we regard paradigms as special cases of cognitive norms, then we must perceive innovation and discovery in science as special cases of social deviance. (Mulkay :1970a:2)

Mulkay then points out that Kuhn makes an important distinction between the paradigm that guides a scientific community, and the rules. Kuhn has argued that paradigms can guide research in the absence of rules, although rules are frequently derived from paradigms. The paradigm is a particular achievement, and it is partly this, Mulkay suggests, that makes it unamenable to sociological analysis. Kuhn mentions four types of rules:

1. Explicit statements of scientific laws, concepts and theories, which Mulkay wishes to call cognitive norms.
2. Commitments to instrumentation and its uses, which Mulkay wishes to call technical norms.
3. General commitments and beliefs about types of theory and entities.
4. Very general assumptions -- for example that the world is regular.

Mulkay suggests that Kuhn never explicitly tells the reader how rules derive from paradigms. Mulkay rules out the proposition that paradigms must come first in time, since he suggests that there are occasions when rules (especially types three and four) have "preceded and structured particular paradigms". This suggests that Kuhn means

that paradigms are analytically prior -- they can influence research directly in the absence of rules.¹ Why does Kuhn insist on this? There are four general arguments:

1. Although it is easy to identify the paradigms of mature scientific communities, it is often impossible to specify rules which can be agreed upon by all practitioners in the community. Identification but not agreement is normally possible, and for this reason it is necessary to concentrate on paradigms. To this, Mulkay answers:

Although this argument undoubtedly raises important problems for the sociology of science, I do not believe that it need be accepted in full. First, I can see no reason for expecting there to be a "complete set" of rules shared throughout any scientific community. Indeed it would be a basic assumption of sociological analysis that within any group there will be normative differentiation. Thus it should not be the existence of divergent rules or norms which is problematic but the distribution of these differences throughout the specialty. Second, Kuhn's claim that paradigms are variously reinterpreted within any given specialty indicates that the character of current research in that community cannot be understood by reference to the paradigm alone. The problems which are defined as legitimate and the solutions which are regarded as acceptable will depend, not merely upon the paradigm, but also and more directly on the interpretations of the paradigm actually guiding research. (Mulkay :1970a:4)

Although Mulkay is probably correct on both counts, this is not, in itself, an argument in favour of rule-bound guidance. The "interpretations" in other words, may not depend on rules.

2. Kuhn's second argument for the priority of paradigms is that much scientific knowledge is tacit and often practical, in the sense that it can be understood only by means of participation in applying its concepts and methods to the solution of problems. Knowledge of this kind cannot be expressed in the form of explicit rules. (Mulkay :1970a:4)

1. Mulkay clearly exposes a difficulty in Kuhn's original position, but in this respect it is one that has been largely cleared up in the Postscript, where Kuhn grants that his use of the term "paradigm" varied greatly in level of generality. In the case of specific paradigms, it is not surprising that they should be preceded by rules. In fact, the fourth type of rule mentioned above would necessarily predate any puzzle solving paradigm.

Mulkay agrees with this, but suggests that it is true for all fields of sociological inquiry and not restricted to the sociology of science. The difficulties for the latter are different only in degree, and cannot in any case be resolved by focussing analysis on paradigms, since these can be understood only if the tacit assumptions can be fully explicated. He notes:

It would certainly be extremely difficult, if not impossible, to identify all the assumptions and operations used by particular individuals in their research. It may be much less difficult to specify those shared assumptions which influence the acceptance of information submitted to a given specialty and which thereby constrict the development of its ideas.
(Mulkay :1970a:4)

3. The third reason Kuhn prefers to concentrate on paradigms rather than rules is that paradigms are always present, while rules become explicit at times of crisis. Mulkay suggests that in fact this is similar to the sociological principle that situations involving deviance expose normative commitments that are not otherwise expressed, but none the less exist.¹

4. Finally, Kuhn suggests that concentrating on paradigms helps to make the diversity of specialties easier to understand. Mulkay argues that Kuhn's example involves considerable confusion, as Kuhn argues that paradigms may be shared by a wide range of specialties, yet so may rules. In addition, Kuhn slips into inconsistency by arguing both that:

1. There is an alternative explanation for the explicit formulation of rules in such situations. That is that even implicit rules do not exist under normal circumstances, but that when patterns of behaviour are under attack, the individuals who exhibit those patterns of behaviour formulate them into codes which are, hopefully, more defensible. These codes can be seen as occupying a position that is in some respects not dissimilar to ideological beliefs.

To argue this is not to say that Mulkay's claim is necessarily wrong, but it seems, perhaps, a little premature to conclude that clear sets of rules can be abstracted from all aspects of scientific behaviour because at times of crisis they evolve and can be clearly stated.

the paradigm of quantum mechanics determines several research traditions and that it is transformed into a new paradigm within each specialty. (Mulkey :1970a:5)

Although Kuhn is loose in his use of language, a close reading of the relevant passage suggests that Mulkey has misunderstood the import of his argument. Kuhn talks of widely shared laws of quantum mechanics, which with a number of different exemplary applications form a number of paradigms of quantum mechanics. The import of this passage is not to suggest that there is a widely shared paradigm of quantum mechanics.¹

Mulkey thinks that there would be less likelihood of confusion if one thought in terms of cognitive norms rather than paradigms. He writes:

Instead of first identifying a paradigm we would attempt to locate specific groups of interacting researchers who shared similar cognitive and technical standards. This combination of social and "intellectual" criteria would reduce the danger of our regarding all those who "shared the same paradigm" as a meaningful unit of sociological study. (Mulkey :1970a:5)

Kuhn might argue in return that those who shared the same paradigm were, in fact, a meaningful unit of sociological study, and certainly those who shared an exemplar would be the sort of interacting group a detailed study of the fine structure of science might reveal.

Mulkey's suggestion is similar to Kuhn's most recent proposal: that interacting networks should first be discovered, and then shared standards can be elucidated. One problem with Mulkey's approach is that it is not clear how easy it is to elucidate shared intellectual criteria which are not, in substance, similar to Kuhn's exemplars. "What is the norm of research in molecular biology?" is more likely

1. This issue has been more clearly dealt with in the Postscript, where Kuhn talks specifically of "law sketches" and transformation of those law sketches into usable formulae with exemplary applications. It is possible that the basic equations of quantum theory constitute such a "law sketch".

to elucidate a response about the structure of DNA (Watson and Crick), and the genetic code (Crick and Sanger), than it is a description of the rules that guide research. The problem is the same one: what is it that constitutes shared standards?

Finally, Mulkay suggests that many unexpressed assumptions act as normative standards that regulate the acceptable actions of scientists. He writes:

Complete conformity to such norms is of course never found. It must be assumed first that norms always allow a certain leeway, a certain degree of choice, and secondly that other factors, particularly the rewards attaching to conformity, will influence the degree and distribution of conformity.... I suggest, therefore, that no scientific contributions are exempt from a process of social selection in relation to the cognitive and technical norms of particular specialties.
(Mulkay :1970a:5)

The only other reason for giving priority to paradigms in analysis is that according to Kuhn they can be easily identified. Mulkay suggests that this is not in fact the case, because the identification of paradigms may only be possible by referring to shared interpretations.

The first part of this paper represents a two pronged attack on one of Kuhn's most distinctive and fundamental contributions. There is the argument that scientific activity can be seen as being rule-bound in all important respects. Secondly, there is a methodological argument that is in turn composed of two parts. Firstly, in practice, it is impossible to discuss action in any other way, at least at the present time. Secondly, if we look upon scientific action as rule bound, then we can introduce sociological perspectives that have been developed in other areas.

Further discussion of this issue will be postponed to Chapter Eleven, where it is concluded that certain aspects of the exemplar can not easily be described in terms of rules or norms because it is

almost literally nonsensical to have "expectations" about innovations which by their nature cannot be predicted.

In the second part of the paper, Mulkay writes:

If scientific knowledge is to be regarded as normative as well as cognitive in character, the study of scientific innovation becomes equivalent to the study of social control and non-conformity in science. (Mulkay :1970a:6)

Radical scientific innovation, in this view, can be looked on as a special case of non-conformity.¹ Mulkay sees the work of Hagstrom (:1965) as an attempt to develop this insight. Hagstrom was not completely successful partly because he tried to encompass the whole of the American scientific community, and partly because he did not study the relationship between professional recognition and the nature of scientific norms in specialties. A third defect was that he offered no structural account of the sources of new ideas, although he did discuss how ideas are accepted. Essentially Hagstrom hoped to be able to study the scientific community without discussing detailed cognitive and technical norms. Mulkay feels that this is inconsistent with Hagstrom's main preoccupation about the differentiating effects of knowledge.

Since science can be seen as an exchange process, Mulkay proceeds to examine several propositions adduced by Homans (:1961) who divides status groups into three levels, levels which he believes to be inherent in the exchange strategies produced by distribution of recognition. Mulkay summarised Homans' main findings thus:

1. If innovations, and their reception are not fully rule bound, then notions of deviance are less valuable than they might otherwise be. Unfortunately, then, if the view developed in Chapter Eleven is adopted, the second half of this paper is less valuable than it might be supposed.

1. Members of the middle status category are least likely to deviate from group opinion.

2. Persons of high and low status are much more likely to be non-conformist.

3. In established groups, persons of high status are less likely to deviate from more important norms than from less central norms.

4. In established groups, persons of very low status tend to conform publicly but to express little conformity in their private judgements. (Mulkay :1970a:8)

If potential costs and profits are considered, these different tendencies towards non-conformity become comprehensible. Persons at the top of a status ladder value each additional unit of recognition less, and rejection of a single paper is less important to them. For this reason they are more likely to make minor innovations, although radical innovation in a community whose solidarity depends on consensus, and where, in addition the previous contributions of the high status person might be undermined, is less likely. In science, greater cognitive rigidity of senior scientists might reduce their ability to undertake radical innovation, but they might innovate within the already established tradition.

Persons of middle status tend to be more conservative, as they have invested much time in mastering the tradition, but do not yet have a large reserve of prestige. They risk falling in status if they introduce innovations.

For persons of very low status the cost of radical innovation may be very high -- it may result in exclusion from the scientific community. However, once they have been licensed they may be permitted to make "mistakes" which will be passed off as a consequence of youth and inexperience. The cost of radical innovation is therefore considerably less than it would be for a middle status person. In addition, it is

less likely that young scientists will have rigid mental sets. They may be guided by a belief in complete open-mindedness, and they may find that the existing research problems are too trivial to offer much professional profit.

Mulkay finds that many of Homans' suggestions are actually also in Kuhn's work:

Typically, however, Kuhn stresses that innovators are likely to be those whose perceptual framework is less rigid because they have not been fully socialised into the relevant specialty. Although I would not deny that innovation is connected with the extent to which different categories of scientists have internalised current standards, I have suggested above that it also depends on the differential distribution of professional rewards and the way in which divergent exchange strategies are distributed throughout scientific specialties. (Mulkay: 1970a:10)

He suggests a number of ways in which Homans' approach might be applied to the scientific community. There are a great many relevant variables, however, that have not been introduced. Career situation is one -- obviously middle rank scientists vary in career prospects and opportunities. Deviance can only be considered in relation to the perception of norms and standards on the part of the scientist.

Mulkay points out that Kuhn has never completely specified what causes some anomalies to become important, and other potential anomalies to be ignored. He suggests that "anomalies will be ignored when they are comparatively unprofitable" and writes:

that in specialties with a precise cognitive structure very complete consensus can be achieved; that precision and consensus make possible rigorous social control, which in turn promotes detailed investigation within narrowly prescribed limits; and that this focussed research eventually uses up its range of significant problems, as well as generating a series of anomalies. These anomalies become important within the specialty only when the value of "normal" research problems in terms of recognition per unit of research investment, is declining rapidly. In such circumstances the potential profit of resolving one or more of the increasingly prevalent anomalies becomes especially enticing. For the reasons given above, attempts at resolution would be expected to come disproportionately from new entrants. (Mulkay :1970a:11)

There will be differences in recognition patterns between those specialties with well developed and those with less well developed standards. In the former it is easier to see what constitutes non-conformity, and it is possible to judge availability of recognition. Mulkey suggests that solid state physics is an example of such a specialty. Rewards are fairly readily forthcoming in such a specialty, and social control can be maintained through the journals. In solid state physics informal communication was not important, while in high energy physics -- a specialty in theoretical disarray -- there were no obvious indicators as to which were important problems. Pointing to Gaston's work, Mulkey suggests that in such a situation informal communication is more important, since not only does it prevent duplication of research, but it also allows informal definition of important problems. In both cases publication is a ritual, Mulkey suggests. In the first case the acceptable standards are so clear that there is little effective refereeing, while in the second case most findings are known to all concerned before they are actually published.

While all this is speculative, Mulkey none the less believes that a study of different specialties will reveal systematic relationships between cognitive norms and communication patterns.

In the final section Mulkey links up discussion about the likelihood of innovation at different status levels with the cognitive state of the different specialties, and particularly their different availability of recognition. Innovation, he has noted, is more profitable where less recognition is available -- that is to say, in situations of intellectual ferment. If there are few legitimate problems, then young scientists may be willing

to transfer to another discipline, as the costs will be relatively low, and the profits may be quite large.¹ In studies of intellectual migration there has been some evidence to suggest that young scientists move from disciplines with higher cognitive structuring to those with less. He concludes by noting that:

If it could be firmly established that what Kuhn calls 'crisis states' are accompanied by, first, diminishing rates of recognition particularly among those of low status and, secondly, a transfer of such researchers into other specialties, then we would have a strong theoretical link between Kuhn's analysis of growth through revolution and what I have elsewhere termed growth through cross-fertilisation. (Mulkay :1970a:12)

Several questions arise in this paper, and in the conclusion he outlines them. First, if theories of deviance are used to understand innovation, then there must be a way of distinguishing between conforming and deviant contributions. Although such problems may be partially intractable, there are one or two indicators that can be used. Firstly, not all norms are deemed to be equally important. Secondly, those that are peripheral will not be strongly enforced. Here Mulkay implies that there is a 'normative core'. He writes:

... although the cognitive system of a specialty will be complex and undergoing constant development, uniform conformity will be required only to a limited range of scientific assumptions. It follows that only innovations which exceed the limits of these central norms will be strongly resisted. (Mulkay :1970a:13)

The norms that are central to a discipline may be determined by a number of methods:

1. He starts by assuming that less recognition is a function of intellectual crisis, but shifts his ground, and ends up arguing that lack of available recognition is due to the fact that an area gets 'used up'. While it may be true that there is little recognition available in either of these cases, to imply that areas in crisis are used up is mistaken. Two separate mechanisms must be distinguished here. Firstly, there are specialties in crisis, and secondly there are those that are used up in the sense that they contain no interesting problems. Taxonomy, once an important part of the advance of Darwinism, may have become such a backwater.

1. Identification of those contributions which has established a high reputation.
2. A survey of favoured text books, and also of review articles.
3. Concentration on radical intellectual transitions.
4. Examination of new specialties where, for external reasons, the central norms are clearly stated.
5. Study of refereeing standards in journals. ¹

Recently Mulkay has illustrated a thesis about over-production of personnel and innovation in three entirely different social settings: religious innovation in North African Islam; artistic innovation in 19th century France; and the continuous innovation of modern North American Science. He and his co-author write:

Over-production leads to competition as the number of persons eligible for a specific position or set of related positions increases faster than available rewards. Competition leads surplus or under-employed actors to search for new audiences and new markets for their services. At the same time, these actors attempt to modify their products and services, that is, they innovate. Innovation either extends the existing market or creates a new one, thereby fostering new positions and ensuring a flow of rewards. The connection between over-production, scarce rewards and innovation can be discerned in various social settings. (Mulkay and Turner :1971:47)

In the section on modern American science the authors note that the scientific community has grown rapidly and continuously in the USA. Scientific training has been institutionalised since the middle of the last century, but researchers are not systematically allocated to different specialties. This is partly because of geographical and subject spread. They argue that:

1. The first two categories go back to Kuhn's notion of the received achievement and the exemplary form of social control.

scientific apprenticeship syphons the expanding army of new researchers into fairly routine work within existing and well-defined areas of study. If the research community were not growing rapidly this method of recruitment would probably impede innovation. It would tend to foster the gradual accumulation of expected information. However, when combined with rapid growth in numbers, scientific apprenticeship promotes competition which, in turn, assists intellectual development. (Mulkey and Turner :1971:55)

Recognition comes from the contribution of original knowledge, but if there is a great influx of new personnel then there is greater competition for scarce resources. In addition, important problems are likely to be quickly used up. The competition within specialties where technical norms are well specified (such as many areas of physics) leads to three types of innovations:

1. What Kuhn calls normal science (i.e. puzzle solving).
2. Kuhnian 'scientific revolutions'. With diminution of normal scientific problems anomalies become more attractive.
3. The discovery of new areas of ignorance. Specialties are more likely to grow in this way than disciplines, which are more often subject to the Kuhnian processes mentioned above. The discovery of new areas of ignorance leads to the attraction of scientists who are trying to improve their competitive situation.

There is one important respect in which the mechanism proposed for innovation in the other two cases differs from that which is proposed for the scientific community. In the other cases the audience, which received the ideas or innovations was separate from the producers or innovators, while in the case of science this is not true. The scientist is both producer and consumer of ideas. This fact, the authors suggest, is perhaps responsible for the intensity of scientific innovation, since each contribution alters the market situation unfavourably for the scientist -- and thus

forces him to yet further innovation. The authors conclude by pointing out that they have not examined all the relevant details about the process of innovation. Thus, the content of the knowledge has been largely ignored, for example. They view their study as a first attempt to show that certain general processes involving over production, competition, and specialisation, are involved in the innovatory activity in certain circumstances.

The most recent paper (Mulkey and Williams :1971) refers to some earlier research at the Physics Department of the Simon Fraser University. The study is concerned with the recognition-information exchange system, and in particular, the manner in which the reward system structures action in the department. The authors show that the physicists in the department were able to maintain professional autonomy in the sorts of problems that they chose for study, because of the policy of the Canadian National Research Council was to fund all good work. This freedom was supplemented by the norms of individual independence that the researchers found in the department.

How, in fact, did the physicists determine their research goals?

On this the authors wrote:

The basic research goal of all the physicists at S.F.U. was that of contributing something new to the body of scientific knowledge. This goal can be interpreted as a product of conformity to the norm of originality described by Merton.

(Mulkey and Williams :1971:71)

None the less, absolute originality was not enjoined:

... although the physicists we studied wished to produce original results, their originality was limited by the paradigm accepted within their specialty. Originality is not valued unconditionally in physics. It is valued only in so far as it contributes to the extension or modification of the current paradigm. (Mulkey and Williams :1971:71)

There was general agreement among the leaders of the specialty of solid state physic (in which area the members of the department all worked) that the basic 'ground rules' had been laid down, so there was also general agreement about what constituted important problems. As a result, the competitive situation was rather fierce and this showed itself in a concern about anticipation in research publication. Scientists may get round this in four ways. Firstly they establish informal communication networks in order to avoid duplication of work. Secondly, they work on difficult research problems, which reduces the number of competitors, and the need for information from others, and also results in high recognition if the outcome is successful. Thirdly, a scientist may work on the margins of the discipline (although this may lead to competition with other workers in other disciplines) and fourthly, the presentation of results may be speeded up in order to reduce the chance of anticipation. The authors mention actions of solid state physicists under two of these headings. A few scientists had chosen difficult problems for the reason given above. However, none would admit to speeding up publication, and they tended to be rather critical of the idea. The more senior physicists tended to be less worried about anticipation and competition, partly because its effects were less severe for them, and partly they could avoid competition by developing informal communication patterns, by working on difficult or interdisciplinary areas that became more visible to them as they got older, and by getting larger grants than those down the scale.

In the next section the authors compare the proposition that recognition (and thus publication) are a result of conformity to technical norms, with the view held by Storer and others, that they

are as a result of conformity to social norms. They examine, in particular, the social norms of universalism and organised scepticism, and find that the norm of universalism is not followed in the refereeing system. Thus, referees know the authors of the papers which they referee. Again, despite the refereeing system, many of the papers published were held to be of very low quality -- many of them were even wrong. There are two possible reasons for the belief that the quality of papers was low. Firstly, it was possible that there were no well established evaluative criteria, but this was not the case in solid state physics. Secondly, it might be that:

the obligations of refereeing are not fulfilled because they are not rewarded with professional recognition.

(Mulkey and Williams :1971:74)

The authors agree with the second proposition, since it was clear that in many cases the scrutiny of the papers by referees was very superficial. They checked for the style of presentation, for correct use of techniques and for slightly different or novel results. The anonymity of the referees made it less likely that they would carry out their obligations, and in some cases this anonymity protected the referees in actions that were completely dishonest -- the use of data and information gained through being sent papers to referee.

In the case of organised scepticism, the authors wrote that:

Our findings do indicate a slight tendency for organized scepticism to exist as a norm. But even more conclusively they show that the norm had little influence upon the actual behaviour of our respondents, none of whom had ever taken steps to criticize publically the poor work which, they stressed, filled the journals. (Mulkey and Williams :1971:75)

Criticism of other work was not highly valued, and it was rarely

undertaken.

Mulkay and Williams next consider other types of reward, concluding that money was relatively unimportant compared with the freedom of the worker to choose his own research project. Several of the scientists had moved from industry to university, and suffered a drop in salary, in order to have this freedom. They never took out patents, partly because they did not think that greater recognition would result, and partly because taking out a patent meant delaying publication, and hence delaying recognition from the scientific community.

They also consider the teaching role, which they see, in the case of the physics department, as being geared into the professional goal of research, rather than a number of other possible goals. The decision to concentrate on a few, high quality students, was at variance with the aims of the university, at least as expressed by politicians and educationalists, and there was a widespread belief that promotion depended much more on research than teaching performance, even though formally they were both given equal weight.

In a final section the authors consider the structure of authority relationships in the department. They note that in many university departments autonomy is maintained by some sort of democratic structure, yet they write of the Simon Fraser Physics Department that it:

... was accurately described by some of its members as a 'benevolent dictatorship'. It was a dictatorship in the sense that administrative decisions were made and departmental policy promulgated by the full professors and, more specifically, by the Head. It was benevolent in the sense that departmental opinion was regularly probed through informal discussions and, more significantly, in the sense that there was general agreement about the proper goals of the department and the means to be used in attaining them. (Mulkay and Williams :1971:79)

The authors suggest two reasons why the departmental structure took this form. First, most of the members were so concerned with research that they were happy to be able to avoid an administrative load. Secondly, so high was the agreement about goals and policies that it was not, in one sense, necessary to have a more decentralised authority structure. Mitigating against the latter was one factor -- the distinction between theoreticians and experimentalists. In the department this distinction manifested itself in three ways. Firstly, with the exception of the Head of the department, no theoreticians and experimentalists collaborated in publication. (This can be explained by suggesting that the two groups were addressing two different audiences with different paradigm induced standards.) Secondly, there were informal groupings in the department, which divided the experimentalists from the theoreticians. Thirdly, there was 'some slight evidence of negative feelings between the two groups'. These divisive tendencies were counteracted by integrating factors. Firstly, the language barrier between the two groups was low -- unlike, for example, high energy physics. Secondly, the two groups undoubtedly influenced one another in their interests. Thirdly, the Head of the department was both an experimentalist and a theoretician.

10.411 Summary

Mulkay's position is as follows:

1. The content of science has both cognitive and normative status.
2. The knowledge, and all other important aspects of Kuhn's

paradigm, can be described in terms of norms.¹

3. Following from the above, scientific innovation can be seen as deviance under many circumstances, since it breaks norms.

4. There is a central concern, not only with social control, but also with innovation and its sources. One mechanism considered was that of competition for limited positions or rewards. If rewards were limited, then there was an incentive to innovate, create a new market, and hence improve competitive situation. He wishes to establish such relationships as exist between competition for recognition or position, communication networks, and cultural innovation.

10.42 Barnes and Dolby

Barnes and Dolby have followed a line similar to that of Mulkay in their recent work. They too have reviewed the Mertonian social norms of science, and outlined some of the claims that have been made for this approach. They write:

It is our view that the practice of treating science as an homogeneous institution typified by the pure research of the university will rapidly decline. What is more interesting is the adequacy of the Mertonian approach with respect to 'pure' science itself, and it is on this that we shall concentrate, our aim being to show that Merton has failed to identify a constant, specific, overriding normative structure within which this activity occurs. (Barnes and Dolby :1970:7)

They note that Merton's justification of the proposed norms is

1. Mulkay reinterprets Kuhn's work in terms of norms perhaps because, like other sociologists, he has been taught to think in terms of norms when considering systems of social control. It requires a conscious effort not to slip into this way of thinking. In fact, the debate is not simply one that should be confined to the sociology of science. In innovative situations (such as science, case law, etc) an exemplary system of social control may exist. The problem at present is that if the system of social control is normative then the whole sociological apparatus can be used in discussing social control. If the system of social control is exemplary, then the way in which it works has to be understood from scratch. This issue is further discussed in Chapter 11.

threefold. First, the norms can be seen in "writings of the scientific spirit". Secondly, scientists are guided in their actions by the norms, and thirdly, the norms are positively functional for the goals of science. Barnes and Dolby make a distinction between 'professed norms' and 'statistical norms', and suggest that Merton has concentrated on professed norms in a situation where these differ markedly from statistical norms. They note:

In the light of this we shall frame our criticisms into three sections:

1. We shall argue that scepticism, rationality and universalism cannot represent statistical norms specific to science.
2. In the light of a brief historical account we shall argue that professed and statistical norms within science vary over time.
3. We shall critically consider Merton's description of scientific ambivalence, and here will stress the importance of the way in which the sociologist describes norms; different abstract descriptions of the same rule-governed behaviour can lead to strongly varying conclusions. (Barnes and Dolby :1970:8)

The three norms mentioned above are supposed to represent institutional limitations on possible courses of action open to the scientist. They represent a common 'scientific approach' independent of the content of science. The authors suggest that in fact these norms fail to 'provide distinctive general rules which discriminate between alternative courses of action for scientists'. Rationality refers to adherence to a set of rules that are universally found in our culture, and the scientist has no special rules of rationality. If this is so, then rationality is not a distinctively scientific norm. Universalism is another case in point -- all societies have prior truth criteria of an impersonal nature. The authors distinguish between criteria of truth on the one hand, and indicators of truth on the other, and suggest that Merton fails to make this

distinction. Merton argues that scientists demand that truth claims be "consonant with observation" while suggesting that in other parts of society attributes of the person making the claim are more relevant. They believe that this is mistaken:

We would argue that when, for instance, a Nazi stated that non-Aryan science was bad he was making an empirical claim, not uttering a tautology. That is to say, he was using race as an indicator of bad science, which latter he defined in terms of the same criteria of truth as anyone else. He was making a mistake, not using a set of separate standards. The form of this behaviour is analogous to that of the scientist who scans the journals reading articles by 'big names' only, or who learns to avoid the work of certain known incompetents.

(Barnes and Dolby :1970:9)

The authors next discuss organised scepticism, which they contrast with the position adopted by Kuhn. They suggest, like Mulkay, that the positions of Merton and Kuhn are, in this respect, incompatible.

In the second section of the paper they make a brief survey of the institution of science at three times:

1. In seventeenth and eighteenth century Britain, when it was mainly an amateur occupation.
 2. Professional science in France, and then on a larger scale in Germany, in the nineteenth century.
 3. Twentieth century 'big science' which depends on societal support, and justifies itself in a number of pragmatic ways.
- They suggest that the character of scientific action has varied very greatly at different times, and concentration on professed norms has led to a mistaken emphasis on the stability of certain central norms, and has underemphasised the respects in which the institution has changed.

In the third section of the paper they discuss a number of cases of

sociological ambivalence which have been identified by Merton and Barber (1963). Sociological ambivalence is defined by Merton as: incompatible expectations, beliefs and attitudes associated with a single role, or more generally to a set of roles. Barnes and Dolby note that:

Since these norms cannot be simultaneously expressed in behaviour, they come to be expressed in an oscillation of behaviours. (Barnes and Dolby :1970:18)

Merton has suggested that institutions tend to be defined in terms of pairs of conflicting norms. Barnes and Dolby do not think that this is true for science, and suggest that the "conflict depends on the way Merton states the norms". They mention, for example, the dichotomy set up by Merton:

The scientist must be ready to make his new found knowledge available to his peers as soon as possible, BUT he must avoid an undue tendency to rush into print. (Merton :1965:113)

Barnes and Dolby describe the second of these norms as:

too value-loaded to be in any way descriptive; what does the term "undue" signify? The only interpretation we can suggest is that there is a strong likelihood that a firm belief is incorrect, i.e. not knowledge at all, then to rush into print with it is undue haste. But on this interpretation the norms formulated above are not contradictory. (Barnes and Dolby :1970:19)

They doubt whether norms of this sort are internalised at all, and suggest that there are technical norms which guide scientists in their actions with reference to publication, and lead them to avoid either of the extremes posed in the pair of norms described above.

Another ambivalence discussed by Merton concerns priority, where he sees the operation of two incompatible values: originality and humility. Barnes and Dolby agree that this causes stress in scientists, but do not feel that this is for the reason that Merton puts forward. This ambivalence, they suggest, revolves

around the fact that something close to a system of private property has been established, although not without difficulty, within the institution of science. It was necessary, in the case of priority disputes, to develop better institutionalised means of establishing a claim to priority. Yet, with the growth of science, the chance of simultaneous discovery has not decreased, and has even increased. It is less clear what it is that constitutes a discovery, partly because it is clear that any discovery is the result of the work of many people. The authors imply that other methods of recognition have become institutionalised -- the circulation of preprints, or working papers, with half baked ideas. Barnes and Dolby Believe that:

changes are not only occurring within the recognition system but also to the recognition system. (Barnes and Dolby :1970:23)

Merton would accept the former, but not, presumably, the latter.

Barnes and Dolby conclude the paper with a brief discussion of some of the implications of their thesis. They write that:

Within the highly differentiated societies of today social order can be maintained by specialised agencies independently of a total normative consensus; real communication and meaningful interaction can occur between groups with widely differing practices and values. Such groups always seem to have existed in science: to put it briefly, normative consensus and cohesion within them have made for the efficient information exchange and cooperation invaluable in the development of science, whereas differences between them help to explain conceptual innovation and the development of the theories or disciplines. (Barnes and Dolby :1970:23)

The sort of normative consensus upon which such groups are based derives from the technical norms of the paradigms. If these are stressed, then Mertonian notions of the "ethos" of science are not necessary, and it is possible to adhere to the norms of science, and yet hold other political and religious views. They mention the situation of competition between two paradigms, and the fact that

the one that is perceived as being more successful will attract the majority of recruits -- stressing that scientific change is a social as much as a psychological process. Debates between two paradigm groups depend to a large extent on concepts and ideas drawn from outside the individual paradigm. While appeals to ideal norms such as rationality often occur in this kind of situation, they do not think that such appeals should be abstracted from their polemical context.

Finally, they note that there is considerable variation of normative structures over the scientific community, but that potential conflict is reduced by the structure of scientific institutions. Sanctioning power is limited, and most scientists are not totally within the power of others. The authors conclude with the following:

We would suggest that in addition to functionalist premises another element in Merton's theoretical position has contributed to an inordinate stress on overriding scientific norms: this is a tendency, in analysis, to treat every institution as a micro-society with problems of integration identical to those of a total society. The nature of our disagreement with this view should by now be clear. (Barnes and Dolby :1970:25)

While Barnes and Dolby cover much the same ground as Mulkay, there is at least one important difference -- they have reservations about translating all the important parts of paradigms straight into sociological language, and ascribing them normative status. For Barnes and Dolby the technical norms are seen as coming from the paradigm. For Mulkay the paradigms appear to constitute the norms of scientific action. Barnes and Dolby are unwilling to take this step -- a step that has already been discussed in the survey of Mulkay's work, and will be considered further in Chapter 11.

10.43 Mullins

Mullins has shown a consistent interest in the interrelationships between the social networks and the cultural structure of science. This interest was first developed in a study of 248 biological scientists (Mullins :1966; 1968), in which informal network structure was investigated, and some of its main correlates, both structural and cultural, were determined. Since then he has worked on the "phage group" of molecular biologists (Mullins :1968a; 1971), seeking to show how the social structure of this group has developed parallel with the culture.

10.431 1966

In 1966 he surveyed the literature on informal communication in the sociology of science and wrote:

The findings of the four major works on informal communication suggest that informal communication is necessary to the advancement of science, and that informal communication consists, in part, of information not available elsewhere. (Mullins :1966:23)

A pilot study that involved interviewing a number of biological scientists, led him to a number of conclusions. Firstly that:

the scientists participated in two different sets of social relationships having different functions. A number of respondents referred to these sets of relationships as "grapevines". The first "grapevine" spreads reports of job changes, awards, and a general idea of what other scientists are doing. This grapevine seems to include almost all scientists ...

The second grapevine involves contacts among fewer persons, i.e., those who are interested in a particular research problem or orientation. These contacts are usually one-to-one and involve current research findings, interests, and problems. (Mullins :1966:29)

The second grapevine with which he was mainly concerned, allowed transmission of unpublished findings, new ideas, and materials. A lag between the time new knowledge appeared on the grapevine and the time of its publication, sometimes made entry into the research

field difficult for the outsider.

He went on to write:

Because culture is the fundamental content of communication, culture is also important to this discussion at the level of communication content. If science is a social structure for the purpose of developing, maintaining, and transmitting content, then it is a social institution with cultural primacy. (Mullins :1966:36)

He found it difficult to understand the social meaning of specialty labels, noting that these did not necessarily distinguish discrete and stable social groups. Scientists also had difficulties in defining their own specialties, or those of their colleagues. Some names tended to be more inclusive, and others less so, and many were used as "contrast sets", to emphasise distinctions perceived as being important. He drew an analogy between Kuhn's "paradigm" and Levi Strauss' "totemism", arguing that:

Those who share a paradigm are a grouping. Two scientists will use paradigm difference to describe the differences between them. This use of paradigms to define which social groupings are close and which are distant permits the scientist to order the social world by ascribing greater or lesser similarities and differences to persons who are nearer or farther in a social sense. Rapid redefinitions are possible with this type of system. (Mullins :1966:41)

To enter a specialty it is necessary to be legitimated, either by actually publishing in the area, or by being the student or colleague of a member of the informal network.

Next, Mullins defined his attitude to the relationship between social structure and culture:

The cultural organization of science is closely related to, but not descriptive of, its social structure. The social relations among persons, although they are spoken of in terms of cultural (paradigm) differences, are the specific interest of this thesis. The relation of social groupings to their paradigms will be assumed to be subsidiary to their inter-relations among social groupings.

Social groupings are not to be considered causative of paradigm groupings. The possibility of complex interactions

between paradigms and social relations certainly exists, but for this thesis, the primacy of the social relation over the paradigm relations (or such indicators of the paradigm relations as exist) will be assumed.

The background for this decision is the belief of the author (based on the difficulties outlined above) that there is no systematic approach to the cultural organization of science which will permit an examination of the organization and communication of research. One could, using anthropological field study methods, develop a description of the cultural structure of some segment of science. First, however, a description of the pattern of social organization must be given if the concept "segment of science" is to have meaning.
(Mullins :1966:43)

Like Hagstrom (:1965) and Kuhn, Mullins assumed that the best judges of a piece of work in a specialty are the other members of the specialty. If the innovative piece of work reduces the tension caused by some unsolved problem, then they are likely to support it. At the same time, the acceptance of an innovation may cause strain in a group which had depended on a basis of agreement which has now been undermined.

In his empirical work Mullins used a number of concepts: the discipline of training, the discipline of occupation, and the discipline of orientation of the actor. These he defined in a social manner. While the discipline is "a major division of research or theory", the departmental structure of the universities represents "the institutional fossils of the intellectual taxonomy of times past."

The relationship between the discipline and the department is complex:

This relationship is based on the fact that university departments are primary sources for the identity of disciplines. In the modern setting, they are the source of the education that creates disciplines of training. They are the locations to which a scientist interested in a discipline of orientation would look for like-minded scientists. Culturally speaking, a new discipline is created largely by the recognition attached to the creation of new university departments bearing the name

of the new discipline. (Mullins :1966:64)

The term specialty, has both a social and cultural meaning. Socially, it refers to that group of scientists working in the same area, with whom the individual is in contact. Culturally, Mullins sees it as a set of research problems that are thought of as belonging together. After a discussion of his use of the terms "network" and "communication", he introduces the term "orientation". He writes:

Orientations are the central cultural focus of this study. An orientation is an approach to, or a viewpoint on, a specific subject. In this study, the specific subject is the research in which the scientist is most involved at the time when he completes the questionnaire. The specific orientations are a set of possible dichotomies. (Mullins :1966:71)

The distinctions that he makes are (1) chemical-physical, (2) disease-basic process, (3) structure-process, (4) energy-control, (5) substantive-technique, and (6) concerned with growth and development-not concerned with growth and development.¹

Mullins then discusses the term "paradigm" emphasising its exemplary aspects, and mentioning in particular, Kuhn's term

1. These orientations do not offer a full definition of the actor's paradigm. The question is, are they sufficiently sensitive for the purpose Mullins has in mind? He wanted to compare respondents' definitions of "my research" with their colleagues' definitions of "my research", in order to discover the degree to which the orientations differed. While recognising the limitations of this approach, he wrote:

The interest for this study, however, is to produce a definition that relates to basic issues raised in an approach to the biological sciences. (Mullins :1966:74)

It is possible that there may be two schools which have the same basic problem and the same orientations, but which attempt to answer the problem in a very different manner. It is clear that this would not be detected by the orientations. However, since it is unlikely that scientists will mention others with whom they radically disagree, this is not very likely to have occurred in his sample. None the less, the indicator is open to this weakness.

"model achievement". He agrees with Bentley Glass (Glass :1963) when the latter argues, in effect, that a situation of "revolution in perpetuity" may have become the normal state in biology. Then he suggests that since Kuhn argues that a paradigm guides the scientist in making decisions about firstly, whether and where, and then secondly, about how to carry out his future work (Kuhn :1963), it is in the latter that the orientations are most important.

He writes:

In the case of orientations, the decision to begin research has already been made; thus the function of the paradigm has been, at least partially, fulfilled. The scientist in his research is already beginning to concern himself with communicating the basis of his research. In this shift to communication, the important elements are (1) the terms which have been defined, i.e., "placed in semantic space" and (2) the outline of that space. (Mullins :1966:75)

Unfortunately, it is not clear how closely his orientations relate to the above. He is on surer ground when he discusses models, which he regards as being a set of concepts or objects used for communication. The model is communicable, whereas the paradigm is not. It is for this reason that, in his view "orientation similarities in this research ... are at best indices of paradigm similarity".

Out of analysis of the networks he came to several conclusions:

... these scientists' social relations tended strongly to be between those who perceived their research in the same way, on each scale and for all scales. Since these paired choices are basic to the social structural elements under consideration, this similarity of description demonstrates that, for this population, social structure and cultural orientation are very closely related. (Mullins :1968:788)

He goes on to show the degree to which pairs of workers and other strongly related groups are drawn from members of the same social status. Although most respondents chose scientists that

were similar in status ¹ there was none the less much variation. Overall, there was no significant tendency to chose scientists who were of very much higher status, and neither the discipline of orientation, nor the discipline of location (or department) appeared to be at all relevant to the structure of the network.

He goes on to note that discrete specialties, that are discussed by Hagstrom and perceived by many many scientists, do not seem to occur in his data, as the network of informal communication seems to ramble across the whole face of biological science. This may be either because the data are not good enough to identify such specialties, or it may be because specialties as such do not exist.

Finally, he speculates about ways in which networks may grow up, with members sharing a set of orientations. A scientist may speculate out loud at a meeting, and reveal a novel orientation. If others are present with substantially the same set of orientations, then a new network may develop, with its own orientation. It will either show successes, in which case it will attract new personnel, or it may not, in which case it may decline and go out of existence. In contrasting the fairly rigid formal organisation of science which exists at present, with the more fluid organisation that existed before 1850 (a point raised by Ben David (Ben David :1964)), he notes that the networks that he has discovered show similarity to the characteristics of pre 1850 science. He writes:

The above-outlined observations would appear to be a prima facie case for establishing "Grapevine Two", identified earlier in this chapter with the networks of relations which

1. Status is defined in three rough senses -- organisational, professional, and in terms of seniority in the specialty.

developed in this research, as the revolutionary groups that are the focus of Ben David's interest. Certainly the biological sciences are undergoing a revolution, or have undergone one very recently. (Mullins :1966:200)

10.432 1966: Discussion

In this early study it is clear that Mullins is influenced by a number of factors. Firstly, he is clearly not strongly influenced by the work of Merton. His formal analysis of networks comes from The Proceedings of the International Congress on Scientific Communication in particular (National Academy of Science-National Research Council :1959), and his concern with the social structure of science is influenced by de Solla Price (Price :1961; 1963).

Secondly, he is strongly influenced by Kuhn (Kuhn :1962; 1963), and this leads him to an interest in the knowledge of science. He does not develop a sophisticated understanding of knowledge in the biological science because his snowball technique leads him to cover a wide area of science.

However, within the limits set, this study is important. It shows that informal networks parallel cultural structure in science, although the nature of the interrelations are not clearly spelled out. It also shows that disciplinary structures and status differences are not strongly relevant for the development of informal networks.

10.433 1971

The most recent paper (Mullins :1971) opens as a criticism of the model of role hybridisation advanced by Ben David (Ben David and Collins :1966). They argue that ideas must be picked up and developed systematically as the end product of a social role, if they are to become well developed, and a new discipline is to emerge. One possible manner in which this may occur is through

role hybridisation, which involved bringing the methods of one role (role A) to the subject matter of another role (role B). In this way a new occupational role is developed. In the model of role hybridisation, it is necessary to postulate that Role A is of high status, but career chances for those who occupy it are poor, while Role B is of low status, but the career chances are much better. Although personnel would not normally consent to move from Role A to a lower status role, in view of the poor career chances, certain practitioners may be willing to create a new role of intermediate status, Role C, by introducing the techniques of Role A to the subject matter of Role B. The reason for this is that by so doing they hope to improve their career chances. Ben David and Collins claim to show that this situation occurred in the formation of scientific psychology in Germany in the nineteenth century.

Mullins notes that this model has already been partially undermined by the work of Fisher (:1966; 1967) who shows that not only is it necessary for practitioners to have students, but also that:

... its practitioners must have students at the time they are working on its problems. Further, new members of that specialty (followers in the Ben David-Collins model) must also be in a position to have students. (Mullins :1971:3)

The general point is that the forerunners, founders, followers distinction developed by Ben David is too simple, and the question of continuance must be considered for each generation, even in the case of an institutionalised specialty. Mullins continues:

This paper extends and supports Fisher's findings. It shows that the Ben-David -- Collins model is insufficient to explain phage work's development into the specialty of molecular biology. Even though (1) persons in a field of high academic

standing (physics) did decide to enter one with lower academic standing (biology) and (2) some recruiting of students did occur, these factors were not sufficient to establish this specialty, particularly given competitive modern conditions. Further, the Ben-David -- Collins model is not necessary in that a full account of molecular biology's development can be given by using normal processes that ordinarily occur in science; we do not need recourse to any special concepts such as role-hybridization.

These normal processes are (1) paradigm development, (2) problem success, and (3) "puzzle solving" (all intellectual processes), and (4) communication, (5) co-authorship, (6) collegueship, and (7) apprenticeship (all social processes). (Mullins :1971:3)

The scheme that Mullins develops, which is a four-part one, appears to be drawn partly from a paper by Stent (:1968). He is concerned with both social and intellectual development:

The social model includes four stages: (1) paradigm group, (2) social network, (3) cluster, and (4) specialty.
(Mullins :1971:5)

While these are clearly defined, less clearly defined are the parallel intellectual processes. He suggests that Stent's three part distinction between the romantic stage (1935-1953) (a stage that Mullins later divides into (a) paradigm group and (b) social network), the dogmatic stage (1953-1962), and the academic stage (1962-present) may be paralleled by the processes of paradigm development, success, and puzzle solving, but the distinctions between these three categories, which are a clear extension of the basic ideas of Kuhn, are not immediately self explanatory. It is in the detailed study of the work on phage that such distinctions become clear. Mullins writes:

It should be emphasized that these divisions are artificial in the sense that, for any given intellectual problem, they can overlap. Paradigm and network type structures in particular continue to form and function even after a group has entered the cluster or specialty stage. Their function at that point in time is usually to feed new members and ideas into the increasingly formal cluster or specialty, although occasionally a totally new cluster will result. Discussion of each stage is

not intended to imply that aspects of preceding stages are no longer functioning, only that, for a given intellectual problem, at least this much more social structural progress has been made. (Mullins :1971:6)

Paradigm Group. Of this Mullins writes:

(this) is the absolute minimum that can be considered a scientific group. Its members have no necessary social connections. Kuhn's work indicates that any useful paradigm must, by definition, be the property of some social group that is utilizing it. He is not clear, however, about what such a group might look like or who it might include. The minimum expected of such an entity is (1) more than one established scientist (by definition; it is a group) that (2) have shifted from one viewpoint to another (gestalt shift), and (3) whose members may or may not be in communication with one another. (Mullins :1971:7)

The group of individuals in a paradigm group should "have moved into a similar cognitive situation with respect to the same or similar problems", and he is prepared to allow actors with quite disparate cognitive situations into the paradigm group. He names not only the phage group itself, but also biochemists, geneticists, structural chemists and X-ray crystallographers. All of these and others:

... were also trying to determine the structure and function of large, biologically interesting molecules. These different workers can be considered a paradigm group. All were studying the same basic problem, but they had no particular connection with one another. (Mullins :1971:8)

One might argue that they had very little intellectual connection with one another, and that it is only with the benefit of hindsight that we can see that they came together, gradually, to form the sources of modern molecular biology.

This clearly raises a fundamental problem, for Mullins is obviously right to emphasise that there are "mental sets" which facilitate the development of more extensive collaboration and conceptual unity between previously separate groups. It is, however, not clear that this can be seen except after the event. This implies

that the potential conceptual unity that foreshadowed successful developments will be apparent, but that the conceptual unity that existed, but was never developed into a paradigm or a specialty, will not be apparent. In this approach one has, of course, moved a long way from the actor's point of view.

In an earlier paper (Mullins :1968a) he made a specifically structural definition of a paradigm group. He wrote that paradigm group and:

the social circle are constituted by scientists who use the same reference group. Scientists in such groups show similar citation patterns. (Mullins :1968a:1)

In the most recent definition scientists in the same paradigm group would not be expected to have the same reference groups in general, although they might have one or two individuals in common. In the case of the phage group, it is possible, Mullins seems to argue, that B  hr and Schr  dinger might have been important reference individuals. Their importance was at the most general level, however, transmitting "philosophical" and in fact in some respects competing philosophical attitudes to their followers. It is doubtful whether either Schr  dinger or B  hr were important for the British crystallographers and biochemists who seem, none the less, to have constituted a part of what Mullins describes as the paradigm group.

He is on better ground when he restricts his attention to the phage group alone. He writes:

The group's paradigm, formally stated, became: Studying phages to solve the problem of genetic information transmission with as precise methods as could be developed. This paradigm, like most real paradigms, was not initially very precise, but it would become more precise as time and work passed. A very important event for this paradigm occurred when norms were established to govern the kinds of research done and the manner

in which it was done and presented. (Mullins :1971:9)

He discusses the actual social processes involved when the first scientists (mainly physicists) became involved in phage work. With the establishment of the summer course on phage at Cold Spring Harbor in 1945, Mullins sees the second stage, that of the social network, developing.

The Social Network

The network is a set of numerous pairs and triads of scientists engaged in regular communication or collegueship over a period of time. The pattern of such networks at any one point in time is analyzable, but they are elusive and ephemeral in that they change without much perceptible effect on science. (Mullins :1968a:2)

More formally, the network period "shows two changes from the paradigm period: (1) increased connection among scientists who are working in the area, and (2) a decrease in disconnected or independent persons." During this period (from 1945 to 1953) some of the group's leaders got into a social situation where they were able to recruit students more effectively, the network began to grow, even though the turnover of personnel was considerable, being of the order of 25% per year (Mullins :1971:21). Culturally, although the central problems of the phage group had not changed since the paradigm group period, there were a number of successes. Techniques were codified, and the transfer of DNA was demonstrated. Mullins writes:

Through these and other smaller successes there developed the first elaborations of phage work's paradigm which outlined the terms in which puzzle solving could be done. (Mullins :1971:14)

This, then, is a period when the orientations are very general, underdeveloped, and do not provide a complete guide for action. They are developed and made more specific. Successes in this endeavour clearly feed back into the social structure and help to build a

better connected network.

The Cluster

A cluster forms when scientists become self-conscious about their patterns of communication and begin to set boundaries around those who are working on their same problem. It develops from recombinations of pairs and triads in response to certain favourable conditions (e.g., luck, leadership, a "meaty" problem for research, a supporting institution or institutions). These clusters are often named (externally and/or internally), are more stable than the pairs and triads that form them, have a distinct culture, and are able to draw support and students.

.... it has not yet established formal structures and procedures that will permit it to maintain itself when its informal co-authorship and communication connections change.

(Mullins :1971:22)

The membership of the phage group continued to turn over with some rapidity, and the solidarity of the group was maintained and developed by other means:

1. The group was recognised by others as such.
2. It had "group symbols".
3. Its members had a common life style.
4. They maintained a high rate of interaction with one

another.

The intellectual problems of the group can be seen, Mullins argues, in its symbols. He writes:

Symbols for a scientific group include (1) its view of history and (2) that set of beliefs, theories, etc., which characterizes the group. (Mullins :1971:23)

Between the years 1953 and 1962 the phage group developed and helped to prove the "dogma" of molecular biology -- that DNA is self replicating, it codes for RNA which in turn codes for the sequence of amino acids in proteins; that the code consists of triplets of nucleotides, each triplet coding for a specific amino acid. This model was proved in 1962, but to Delbruck's disappointment

it did not lead to any new laws of physics.

Under the "life style" heading mentioned above, there are a number of items that clearly fall within the area of general scientific culture. These, briefly, were concerned with "research style". Mullins numbers them as follows:

1. The principle of "limited sloppiness".
2. A distaste for chemistry.
3. Publication of few but excellent papers.
4. Theory emphasised over experimental data.
5. Complete intellectual honesty in scientific discussion.

A cluster is, then, a well developed network, distinct from other networks, with its own successful, but still largely unexplored paradigm, and its own "group symbols".

The Specialty

A specialty is an institutionalized cluster which has developed regular processes for training and recruitment into work positions that are defined by institutions as belonging to that specialty. Members are aware of each other's work, although not necessarily deeply involved in communications with one another. They may share a paradigm and a set of judgements about what general work should be done in the area, although the details of those ideas might differ. The specialty, then has many aspects of a formal organization (recruitment procedures, tests of membership, journals, meetings, etc.), and the locations which support its work become much more important than they were to earlier stages.

(Mullins :1971:29)

The social structure becomes institutionalised, and the communication networks centre less around particular people, and the rate of growth of the specialty is much slower than it was at earlier stages. The routinisation also manifests itself in the intellectual and cultural structures. Mullins writes:

The specialty's intellectual problems can be summarised by Kuhn's concept of puzzle solving, the normal activity of science. Kuhn describes puzzle solving as having the following

characteristics: (1) an assured solution; (2) rules that limit the acceptable solutions; and (3) rules that limit the means for arriving at those solutions. This activity is clearly different from the uncertain (with respect to results) research of early phage workers. (Mullins :1971:30)

In his conclusion he asked what constitute important variables which determine the success or failure of the paradigm group to specialty process at any stage. The determinants at an early stage are relatively low level -- a general orientation, the ability to communicate with others with that same orientation, and finally, towards the end, a measure of success in defining problems more concretely, and beginning to solve them. The transition to the cluster stage is more demanding -- he mentions luck, leadership, a "meaty" problem, and a measure of institutional stability. Finally, in the transition from cluster to specialty the competition between universities to support new successful innovations is so great in the USA, that such a transition is possible with the greatest ease.

Mullins then talks about Price's proposition that specialties arise as a result of social engineering, and finds that many influences on the phage group were consciously determined. He concludes that the concept of role hybridisation does not have to be introduced in order to explain the rise of the phage group, and he says that:

Role-hybridization may explain the addition of many new members when a cluster begins to achieve institutional status, but it certainly is of no help in explaining the development of earlier stages. (Mullins :1971:40)

10.434 1971: Discussion

Leaving aside Mullins' tendency to identify the whole of molecular biology as coming from the phage group (a tendency strongly reflected in his main text (Cairns Stent and Watson :1966))

and commented on by Kendrew (:1967) in his review of that volume), and one or two other questions of detailed historical nature, it is clear that Mullins is offering a model through which the development and institutionalisation of new specialties may be understood. There appear to be three main ingredients of this understanding, which are:

1. concern for communication networks, and the way that they change over time.
2. concern with the way in which scientific culture changes over time, and
3. entailed in the two points above, concern with the intellectual and social history of the growth of specialties.

He tends to ignore such exterior 'givens' as the American university system, because, since they are identical for all innovations in science in the USA they "cannot be used to explain the success or failure of particular groups within that set". (Mullins :1971:39) This is not completely satisfactory, since it implies that interactions between specialties are not reflected in those structures. Such factors as hierarchy amongst the specialties and disciplines probably affects the chances of success of different clusters or networks in different ways, and it is likely that these differences are reflected in the university system.

The communication analyses are the best developed aspect of his model:

Intercommunications between scientists are symbolized by four kinds of lines, each representing a type of social activity that continually occurs in science. These activities are (1) communication (serious discussion about on-going research), (2) co-authorship (a more intimate form of association in which two scientists jointly report their research results on some topic), (3) apprenticeship (a student is trained and sponsored

by his teacher), and (4) colleagueship (two scientists work in the same laboratory). (Mullins :1971:5)

Since in his fourfold model, a description of at least the first three stages depends crucially on the nature of the networks, this analysis forms a central part of his approach.. This sort of analysis would seem to be the sort that is recommended by Kuhn in his most recent work (Kuhn :1970a:174). In this work Kuhn does not give specific guidance about how paradigms develop, but rather poses questions about paradigm growth and specialties in specifically sociological terms.

It is incorrect to assume that the model of cultural development proposed by Mullins comes directly from the work of Kuhn. Kuhn does not explain how a paradigm is established in a new area. He rather implies that this and other processes must be studied by "thoughtful empirical investigation". This, however, is far from being a criticism of the work of Mullins. What in fact he does, is to break down the notion of paradigm into three parts -- firstly there is the 'gestalt shift', which is vague, and hardly constitutes a total and effective guide to action. It is not necessarily clear that gestalt shift is the best term in this context, though the general idea is acceptable. Then there is the important variable of success, which concerns the establishment of exemplary applications, which can be worked out in form of symbolic generalisations (Kuhn :1970a:182). Thirdly, and lastly on the time scale, there is the development of normal science puzzle solving, where work is highly determined, and can clearly be seen as puzzle solving. (See Figure 12).

SocialCulturalParadigm group

Group of persons without any inter-communication, possibly holding certain reference individuals in common.

Similarity of orientation in certain general respects. Interested in same general problem.

Network

A set of many pairs and triads of scientists in regular communication or collegueship. The pattern may change easily.

Development of rather more specific scientific guidelines, and a number of successes, possibly of quite small size.

Cluster

Development of a more stable network, which is perceived as being distinct. Recruiting procedures, although informal, are none the less established

Development of specific 'central dogmas', a reinterpreted view of history, and a distinctive research style.

Specialty

Institutionalised cluster with regular processes of training, recruitment, and a corresponding departmental structure. Communication is less intense than at previous stages, but the specialty is much larger. Journals are established.

Final development of routine puzzle solving with most major questions determined. The development of research fragmentation, and consequent loss of distinctive research style.

Figure 12

Model of Growth of Scientific Specialties Proposed by Mullins (:1971)

10.44 Fisher

Fisher is another sociologist who has been influenced by the work of Kuhn. His papers are among the most sophisticated contributions to the discussion about the names of specialties.

He has written two papers on the fate of the Theory of Invariants. (Fisher :1966; 1967). The Theory of Invariants was an important specialty in the late nineteenth and early twentieth centuries, but starting in the 1920s, the amount of activity in the specialty decreased, until today there are very few mathematicians who would call themselves invariant theorists. Fisher, who is concerned with the relationships between the mathematical specialties on the one hand, and their interpretations of the history of mathematics on the other, has shown two rather different things in his work:

1. If the "Theory of Invariants" is taken as a social category in the world of mathematics, then:

as a category its existence is constituted in terms of the opinions mathematicians have about the theory and the actions to which these opinions lead. (Fisher :1967:217)

Since few mathematicians now regard it as an important part of mathematics, it has, for all practical purposes, disappeared.

2. In the second case a study is made of what happened to the men who practised the Theory of Invariants, and its decline is accounted for by its failure to recruit new practitioners.

In the first case, Fisher is concerned not only with the theory of invariants, but also in the manner in which a theory can be used as a division or social classification within the wider body of mathematics. Thus, he writes:

... to an observer a mathematical theory will appear as a vaguely defined locus of activity to which a mathematician refers when he is talking to other mathematicians. If

observations are made over a period of time, or among different groups of mathematicians, then the vagueness increases greatly. Mathematicians at different times and in different places are found to be dividing up their world of mathematics in different ways. In fact, many mathematicians disagree over what belongs to that world of mathematics. (Fisher :1966:137)

Mathematicians view the history of the discipline in terms of an ideology that grows up in their own specialty. It follows that the importance of a theory is interpreted in different ways in different specialties, so, for the observer:

a theory is not a fixed object, but a social category which changes with the changing perspectives of mathematicians.
(Fisher :1966:137)

He continues:

Treating the Theory of Invariants as a social category has several consequences. (1) What is thought to constitute the Theory of Invariants is different for different groups of mathematicians. (2) Different groups of mathematicians evaluate the theory differently within their mathematical Weltanschauung. And (3) these classifications and evaluations evolve over time. The fate of a Theory, when viewed as a social category, is determined by the actions of those who erect it as a category. (Fisher :1966:138)

It follows that there are two groups of mathematicians on whom the survival of the Theory of Invariants depends. Firstly, there are those who associate their names with the theory, who work on it and develop it. If their numbers are reduced, then the continued existence of the theory depends on it being perceived and defined by a second group -- that group of mathematicians who do not practice it.

Fisher discusses the writings of Kuhn, where the latter considers the mythology and history that is built up in a mature, paradigm bound, discipline. He argues that in diverse disciplines, such as mathematics, the specialists themselves will develop such historical interpretations, and these will change as they develop.

He writes that:

Out examination of the multiple characterizations of "The Theory of Invariants" will reveal a number of histories of the subject erected by the invariant theoreticians themselves and by neighbouring specialists. The theory will be seen to die or rather to be relegated to non-existence by a combination of (a) the termination of a "pure" history of Invariant Theory as carried out by invariant theoreticians and (b) Invariant Theory being written out of the histories of those specialties that might possibly be thought of as its heirs. (Fisher :1966:139)

He shows that with the passage of time certain events achieved symbolic status in the rewritten histories. In particular, remarks by Hilbert, although largely ignored at the time, and by no means bringing Invariant Theory to an end, came to have symbolic 'turning point' importance for later generations of mathematicians. He also shows how a major division between advocates of 'construction' procedures, and advocates of procedures of abstraction (which involved members of each group belittling the work of members of the other group), which led to the dominance of those who advocated procedures of abstraction, contributed to the perceived death of Invariant Theory. The Theory had been developed using traditional procedures of mathematical construction. But:

the first really important achievement of the abstract techniques in the field of Invariant Theory is taken not only to be the cause of the death of Invariant Theory, but also a turning point in the way in which mathematics is done. This is an example of the way in which the ideologies of a specialty become, for its members, grounds for the explanation of why certain events occur. (Fisher :1966:140)

Before giving a brief history of the Theory of Invariants, Fisher makes two points. Firstly, he has been very selective in his data, identifying one of the main problems of the theory with the theory itself. Secondly he argues that, for mathematicians, any paper or contribution has immediate implications for much other work. There is a logic of relationship and development that can

only be acquired by much mathematical study. Yet these implications are rarely spelled out in detail, and the way in which a paper 'fits in' is not clear to the outside observer. In this paper Fisher is obliged to ignore this aspect of change and relationship, although he reminds the reader that this has been done by Lakatos (;1963) for a simple example.

He shows that historically there exist elements of five accounts of the later development of Invariant Theory:

1. The 'pure' history of Invariant Theory -- the history as seen by its specialists:

The invariant theoreticians draw a straight line from Boole via Cayley, Gordan and Hilbert to the work that they are doing. They see the theory as growing, sometimes by leaps and sometimes more slowly. With each new contribution the theory widens and there is more to be done. The solution of each problem becomes the grounds for the next. Other theories may make important contributions to the Theory of Invariants, but these contributions do not detract from the theory; they add to it. Invariant Theory is seen as a well established mathematical activity with highly refined techniques that can be applied in a number of different places. Moreover, for them, invariants are deeply imbedded in the progress of mathematics. The theory assimilates new ideas and offers to the mathematical community ideas which are interesting in themselves, but also which, if cultivated, might have wide ranging applications. (Fisher :1966:154)

This is a view that has not been widely expressed since 1930.

2. There is the view of the abstract mathematicians, who look upon the Theory of Invariants as an example of laborious constructional procedures. The theory was swept away (its main problems solved) by Hilbert's development and application of abstract procedures:

Hilbert changed the direction of what problems are taken to be mathematically interesting; before him, Invariant Theory dealt with finding the specific invariants; after him, mathematicians turned to more general problems; now they sought the algebraic properties of systems; this change led to the outmoding of Invariant Theory and the development of "modern" algebra; Invariant Theory as practiced in the spirit of Gordan dealt

with limited problems in a manner which was not conducive to their solution; Hilbert swept away years of unproductive computations by the application of abstract techniques and thereby laid the foundations of modern algebra.

(Fisher :1966:156)

3. In a history of the subject by one of its practitioners, Weyl, who was primarily concerned with the relationship of the theory to groups and the techniques concerning group representations, included many pre-Hilbert techniques, but these have largely been ignored:

... the significant people who pick up on Weyl seem to excise this material completely. They are only interested in what he has to say about group representations. So, as Weyl said, the Theory of Invariants has been subsumed under the theory of group representations. But to his successors invariants have been engulfed in the theory. (Fisher :1966:156)

4. A group who might be considered the intellectual heirs of the theory of Invariants, have included Invariants as a small part of a modern theory. For these people, Weyl was the last classical exponent of Invariant Theory, and the tradition ended with him.

The current research being done stems from the results of modern French mathematics, and on account of its concern with a few peripheral problems, only a handful of mathematicians are interested in it. The name of the problem area is not Invariant Theory, for it only incidentally was motivated by and encompasses problems from that theory. (Fisher :1966:156)

5. Another group, which is very marginal to the mathematical community, do not agree that Invariant Theory is now dead. They see the theory as being quite respectable, and feel that other mathematicians ignore it wrongly.

From these five histories, Fisher is able to develop an account of the death of Invariant Theory as a social category:

1. The "pure" tradition died out because of lack of

recruitment.

2. Others interested in the theory did not convey the interest to their successors.

3. Modern algebraists have cut Invariant Theory out of their intellectual history, despite the fact that many of its hero figures were Invariant Theorists. This may be because of the construction-
abstraction division.

4. Two groups -- those with histories (4) and (5) above -- carry on with some work of the Invariant Theory, but they regard it as either (a) such a small part of their work, or (b) are themselves so marginal to the community of mathematicians, that "they do not carry it forth in a notably visible manner". Fisher writes:

Thus, Invariant Theory is seen to die out because some of its heirs are lost ... , some do not promote the theory ... , while other heirs ... claim part of the subject as an offshoot of the genius of their specialty. The reason these latter claims stick is that there are no invariant-theoreticians around to combat them Therefore, the view of Invariant Theory which has prevailed since 1930 is that which has spread with the growth of modern algebra. (Fisher :1966:158)

The modern algebraists "wrote Invariant Theory out of the picture" and ascribed to Hilbert a role as hero in both the death of the theory, and the rise of abstract algebra. Hilbert's interests changed in 1893, and he wrote at the end of a paper in that year "With this, I believe, are attained the most important goals of a theory of functional fields of invariants". (Fisher :1966:145)

Fisher writes that these sentiments:

if they meant anything, represented Hilbert's personal feelings. In 1893 they were not taken to be pregnant events. But forty years later, when Hilbert is the most famous living mathematician, they are taken to be signs of the death of Invariant Theory. That is, Hilbert's acts take on symbolic meaning. For mathematicians steeped in the tradition of modern algebra, they signify the death of Invariant Theory and, moreover, assume the status of explanations for the theory's demise.

(Fisher :1966:158)

This explanation of the death of Invariant Theory as a social category in mathematics is supplemented by further work in a second paper which shows, by studying the Invariant Theorists, and their ability to attract students, the reasons for the death of the "pure" tradition. Fisher argues that four elements are important in determining the ability of a mathematical tradition to survive:

These are the general environment in which the mathematics is done, the specialists' commitment to the theory, their relationship to their students, and the places in which they worked. (Fisher :1967:218)

Where there is no explicit role of scientist, the advance of science is fitful and slow, and influenced by factors that affect these non-scientific roles. On the other hand, he argues that:

When science is both recognized and supported, the distinct role of 'research scientist' may be embedded in institutions like universities and research laboratories. Then science progresses more rapidly and the continuation of a particular theoretical tradition is closely tied to the relationships between scientific specialties and the career patterns of scientists. (Fisher :1967:219)

Thus, the location of the practitioners may have importance for the maintenance of a specialty.

Fisher argues that change in mathematics is a fairly diffuse process -- more so than in physics, from which Kuhn has normally taken his examples. In mathematics any particular problem is not normally considered basic. A new theory in mathematics is likely, instead of bringing a refutation of an old theory, to lead rather to a shift in interest. Different theories and approaches coexist alongside one another, being practiced in different specialties within mathematics. In order for the theory of a given specialty to maintain itself, it must be capable of maintaining an active research front. The work undertaken is guided by what are felt to

be the central goals of the theory, but in most cases the number of goals increases, and techniques themselves come to be viewed as goals.

Fisher argues that it is possible to account for the decline of the Theory of Invariants by means of the diffuse nature of mathematics (as described above) and certain environmental factors that affected the invariant theorists. The shift in mathematics in the 1920s and 1930s from constructional to abstract procedures resulted in a shift from the problems that then interested invariant theorists -- even though this was only an incidental effect of such a shift.

The problems (that interested invariant theorists) have not been eliminated; they have merely been sidestepped. Therefore, for the invariant theoreticians to carry on their theory they must at least train people in the theory. Beyond that they must maintain the importance and visibility of their theory.
(Fisher :1967:223)

Fisher next considers the importance of commitment to a given theory, suggesting that mathematicians typically work in several different areas during the course of their careers. Therefore, it is not limitation in skills that obliges a specialist to concentrate his interests. It is rather a deep commitment that leads him in such a direction. The location of a mathematician's job is also important, since this is likely to determine whether he is in a position to train students, and pass on his ideas to a new generation. Even if he has access to students, this does not necessarily mean that he will pass on the tradition. His attitude to teaching is obviously very important, as is his personal attractiveness. A charismatic teacher can build up a school and boost a particular theory, while this will not be possible for a less

attractive man.

In his empirical study, Fisher examines a number of the most important invariant theorists in three countries -- Britain, America, and Germany -- and classifies their careers into one or more of the following categories:

1. Marginals: those whose commitment to the theory is small.
 2. Isolates: those who make their living in places not dedicated to the furthering of mathematical research.
 3. Studentless: men who teach where they have the opportunity to train specialists, but train none.
 4. Progenitors: men who train advanced students in the theory.
- (Fisher :1967:225)

An invariant theorist who has students at a time when he is not interested in the theory is unlikely to pass any great interest on to those students. (Fisher classifies such people as studentless). By looking at the biographies of its practitioners in the above manner it is possible to show that the Invariant Theory declined "before any large segment of the mathematical community thought it was no longer interesting".

Fisher then covers the three countries mentioned above:

Britain

1. The major contributors to Invariant Theory, who are great mathematicians, all die before 1900 leaving no effective invariant-theory progeny; those who cultivate the theory between 1900 and 1920 are either isolated, have marginal commitment or are bowed down with teaching responsibilities; ...
2. There are almost no 'schools' in Britain. Aside from the personalities of the men, the environment inhibits them: ...
3. The imagery of Hilbert's having killed Invariant Theory does not effect the maintenance of the theory in Britain. The theory fades away of its own accord. (Fisher :1967:231)

USA

Here Invariant Theory was somewhat more widespread than in Britain. It was possible for 'schools' to develop, but it was not easy to sustain them. So although many students worked on Invariant

Theory, they tended to leave mathematics, became isolated, and stopped work on it. Of the two teachers, one had many other interests, and the other returned to Britain. Once again, Invariant Theory had died long before the "entrance of the imagery of its 'death'".

Germany

Germany unlike Britain or America is an environment which allowed for the establishment of schools of thought. The first generation of invariant theoreticians (Clebsch's) had a number of students who in their turn cultivated the theory within both the German technical highschools and universities. The second generation produces almost no students. Those who have university positions do not seem to want progeny, whereas those in the technical highschools do not have the opportunity to train them. (Fisher :1967:241)

Thus an account of the death of Invariant Theory can be given that is entirely different from that of modern algebraists, who claim that the death knell for Invariant Theory sounded in 1893, with Hilbert's prophetic remarks.

In this work Fisher looks not only at the internal social structure, but he also considers the effects of differences in relevant parts of the external social structure -- the university systems, for example. In addition he discusses the mathematical developments involved in Invariant Theory in some detail. Last, but perhaps most important, he has attempted to understand the relationship between social structure and knowledge on the one hand, and the perceived distinctions of the mathematicians -- that is, the labels for their specialties -- on the other. He has outlined the manner in which history becomes rewritten, and how events which were insignificant at the time, may come to take up a symbolic importance for future generations if they accord with the world view and ideology of those people.

Fisher is clearly indebted to Kuhn, his work being an elaboration or an "articulation" of that of Kuhn. He finds that the structure of mathematics is different in important respects from that of physics, where it is normally possible to find general agreement over what constitute the most important general goals and problems of the community. Mathematics is divided into a great many specialties, whose members do work that may not necessarily be closely related at all. It is unusual for a mathematical theory to be finally refuted, and this is one of the sources of this parallelism. On the other hand, most mathematicians seem to move between specialties a couple of times during the course of their careers, and are interested in more than one field. This accords with the work of Crane and Mullins, who have on occasion argued that there is a seamless web of intercommunication over the whole of science, and that discrete specialties do not grow up.

None the less, the symbolic importance of the name, Invariant Theory, acts as a banner with which workers may identify themselves. Attached to that banner is not only a locus of activity, but also an ideology and a more or less fictional history. When persons no longer carry that banner, it depends on others to ascribe it status, and in the case of Invariant Theory, at least, they failed to do so, and it disappeared as a social category.

Unlike Kuhn, Fisher is centrally concerned about the conditions for the establishment of mathematical research and teaching roles. He shows that there were important differences between Britain, Germany, and the USA in this respect, and that as a matter of fact, invariant theorists were either unable or unwilling to pass the theory on to students, or students were unable to occupy roles

from which they could propagate the theory. As Mullins (:1971) has pointed out, Fisher is more sophisticated than Ben David (and Collins :1966) in his attitude to the master-student relationship. Ben David talks only of the distinction between forerunner, founder, and follower, but Fisher considers the relationship between founder and follower in greater detail and argues, for example, that it is necessary for the founder to be actually working on the theory, and to be interested in students, if the theory is to be successfully transmitted.

Fisher's approach to mathematical specialties is summarised in Figure 13.

10.5 Hagstrom

10.51 Socialisation

Hagstrom's book, The Scientific Community, is primarily concerned with the mode of social control in the scientific community. It is an ambitious work, representing the results of investigations carried out in a wide variety of different disciplines -- physics, chemistry, molecular biology, physical chemistry -- as well as in the "formal sciences" -- mathematics and statistics.

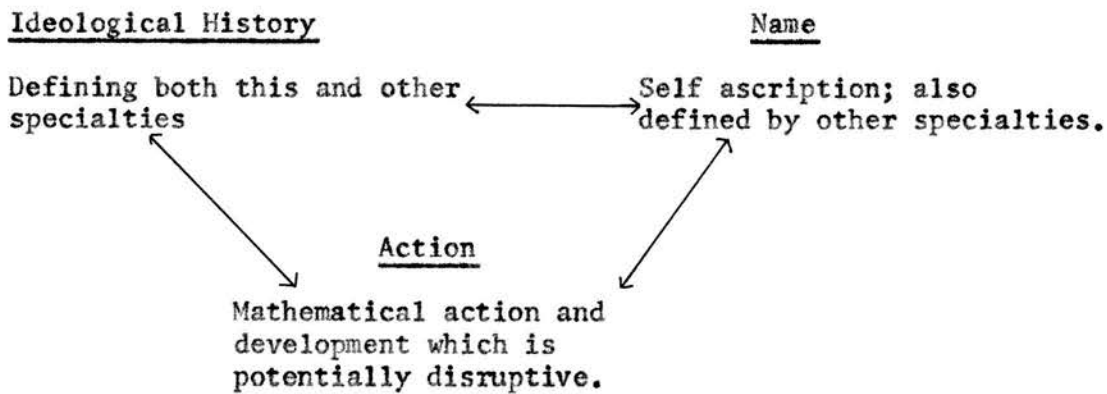
There is a deep ambivalence in much of Hagstrom's work, for although he clearly owes much of his outlook to the Mertonian tradition, he none the less moves close to a position that sees the norms of science as being located in the knowledge -- an attitude of mind that is much closer to Kuhn than Merton. Hagstrom sees most scientists as being strongly committed to certain central values as a result of their training. They are:

Environment
Commitment
Students
Location

all have implications for the

SPECIALTY

which is characterised by:



(There is transfer of both ideas and personnel between specialties)

Figure 13

Major Interests of Model of Mathematics Proposed by Fisher (:1966; 1967)

excited by discoveries, intensely interested in the detailed working of nature, and committed to the elaboration of theories that are of no use whatever in daily life. (Hagstrom :1965:9)

This commitment is the outcome of a long training process, and is reinforced by selective entry procedures, the fact that progress depends on teacher's evaluation, and the development of peer groups. Complex techniques are integrated with the more general norms and commitment mentioned above, and it is in this way in particular, that they are internalised. He supports this proposition with a lengthy quotation from Kuhn, which asserts that scientists do in fact learn detailed manipulative procedures.¹

10.52 Exchange and Recognition

Despite the strong selection and socialisation procedure, Hagstrom still argues that social control must be supplemented by what he calls a "dynamic system". He locates this in the social recognition of discovery. Manuscripts, in his view, are treated as gifts to the scientific community. He develops a discussion about gift systems which owes much to Mauss' book The Gift (Mauss :1970). Gift systems, unlike normal economic exchange systems, are particularly appropriate in situations where many values are held in common. Acceptance of a gift involves recognition of the status of the donor, and the recognition of certain types of reciprocal rights. In the case of science, Hagstrom suggests that information is exchanged for recognition, but this exchange is not publically acknowledged. In fact, most scientists deny that

1. Barnes and Dolby argue that Hagstrom does not succeed in making his point here. For while scientists are certainly socialised into many detailed scientific procedures, there is no hint from the passage quoted from Kuhn, that these are linked up with more general norms of the sort which Hagstrom apparently has in mind.

they seek recognition. On the other hand, failure to recognise a discovery may result in tension -- which comes out, for example, in the form of priority disputes. Hagstrom suggests that the desire to have recognition induces the scientist to write up his results for publication, and in this way he conforms to the scientific norms.

The above is an example of the way Hagstrom makes use of the more general Mertonian norms. He also talks about more specific technical (or Kuhnian like) norms:

Not only does the desire for recognition induce the scientist to communicate his results; it also influences his selection of problems and methods. He will tend to select problems the solution of which will result in greater recognition, and he will tend to select methods that will make his work acceptable to his colleagues.

The range of acceptable methods varies (In the field of mathematics), and most others, the change of standards is one of progress. (Hagstrom :1965:16)

Appropriate standards are not defined purely on a technical basis, but also socially. Thus he mentions a chemist who used a technique that depended on the nutritional requirements of a certain type of bacterium. This was a method, which although perfectly satisfactory, was not altogether acceptable to other biochemists because it depended on the bacteria. In this example Hagstrom does not entirely accept the logic of a Kuhnian position. He assumes that on the one hand there are good technical reasons for using certain methods, but that, on the other hand, intervening social pressures may result in the selection of other, less satisfactory methods. Social and technical imperatives are seen to be opposed to one another, whereas one might argue that technical norms are, in themselves, social.

The processes of recognition seeking also affect the goals of

of a discipline, and the type of subject matters about which authors write. Papers that are strongly deviant may not be accepted for publication, and if published they may not achieve recognition through citation by other authors.

Hagstrom goes on to ask why gift giving persists in science. He suggests that it may actually encourage irrationality by the creation of particularistic obligations. The answer, he believes, is that scientists can be seen as professionals in some ways -- professionals who have a norm that they will serve even though they are not ensured of payment. Their service will always be up to a high, self-imposed standard. The introduction of economic rationality causes the abandonment of moral control. In science it is important to maintain adherence to central moral norms -- in other words scientists must feel responsible for the quality of their gift, and the gift remains, in a sense, the property of the donor. He writes:

... whenever strong commitments to values are expected, the rational calculation of punishments and rewards is regarded as an improper basis for making decisions. ...

Thus, the gift exchange (or the norm of service), as opposed to barter or contractual exchange, is particularly well suited to social systems in which great reliance is placed on the ability of well-socialized persons to operate independently of formal controls. (Hagstrom :1965:21)

This is exactly the situation in science, he suggests.

He sees mechanisms of recognition as falling into two classes -- elementary and institutionalised. Institutionalised recognition comes through formal channels and includes publication in scientific journals, the emulation or citation of a published paper, and the award of honours. Elementary recognition comes through meetings at conferences, visits, telephone calls, and exists between

colleagues. The informal channels usually permit a greater degree of speculation than the formal channels. In addition to the above there is extracollegial recognition, which comes from those outside the profession, including graduate students, non specialists, and the lay public. Such recognition is, however, double edged, being both less important, and of a type that may lead to loss of status in the professional group.

10.53 Competition

Hagstrom discusses the nature of competition in some detail, distinguishing between the prevalence and severity of competition. Prevalence of competition is an indicator of the extent to which frequent anticipation of results, or expectation of such anticipation, occurs. Severity is equivalent to the degree to which anticipation results in a scientist being unable to publish his work. He discusses prevalence and severity of competition in the following terms:

Competition results when scientists can agree on the relative importance of scientific problems and when many of them are able to solve these problems. We can deduce from this that the prevalence and severity of competition will be greater (1) as agreement about the relative importance of problems increases, and (2) as the number of specialists able to attack any given problem increases. A third factor which determines not the prevalence but the severity of competition, is the degree of precision that can be obtained -- the relative degree of confidence specialists may have in particular results. When this degree of confidence is high, replications will be of little value; when it is low, replications may be necessary. Thus, another generalization can be made: (3) the severity of competition will be greater as the degree of confidence in particular research results increases. (Hagstrom :1965:73)

Thus, physics, with generally tight theory and techniques, has both high prevalence and high severity of competition, while chemistry and molecular biology with less tight theory and techniques, although with focussed areas of interest, has an intermediate level

of competition. In mathematics, with tight theory and unambiguous methods, there is severe competition, although with disagreement about what constitutes important problems, competition may be less prevalent.

While competition should lead to selection of the most efficient techniques, and the optimum allocation of research effort, it is not always beneficial as it may lead to "restrictive practices". The reward system constitutes an imperfect market, and the "supply" of research is in any case inelastic.

10.54 Deviance

Deviance may arise in a number of ways. Fraud is unusual, but secrecy conflicts with a norm of free communication, and may result from fear that legitimate use will be made of results. Secrecy may be overcome by enhancing recognition of property rights, and one way of doing this is to develop an informal division of labour. This, however, infringes on the norms of autonomy. Another way of overcoming secrecy is to publish only part of the results, usually in the form of abstracts. But this, in turn, has results that are disadvantageous to science -- it may stop work in the area by others, and it is difficult to know how much reliance to place on results that are reported. If abstracts are not supported by full publication of results, then theorems and techniques may become accepted without any published proof -- they achieve the status of "folk theorems".

10.55 Teamwork

In the third chapter Hagstrom considers teamwork, and its relationship to norms of independence and individualism. He writes:

Norms of independence are very strongly held in science. Three of them can be distinguished. First, the scientist is expected to be able to select research problems freely. Second, he is expected to be able to select freely the methods and techniques to be applied to them. Third, he is expected to be free to evaluate results, to decide himself whether his results and those of others are valid or invalid. (Hagstrom :1965:105)

While the last two are usually taken for granted, it is the first that is usually called into question.

He next develops an explanation, couched in functionalist language, for the existence of these norms, which relates to the process of developing and maintaining professional autonomy. He appears to argue that the health of science depends on respect of these freedoms:

In basic science ... , the selection of problems and the evaluation of the validity of theories are essential parts of the professional task.

Problems are not "given" to basic scientists by others or by "nature", at least in the most important instances. Rather, problems are discovered and invented by scientists. ... The discovery that aspects of nature are problematical is often a central part of the discovery of the solution, and scientists may receive credit for discovering problems even if their own attempts at solution are faulty. In the long run, then, the scientific enterprise depends on the freedom of scientists to select the problems on which they will work.

(Hagstrom :1965:109)

In the short term, however, this is not true, and most scientists are restricted in one way or another, through the existence of departmental structures, and so on. Thus, they may be expected to work on problems which are normally considered to be a part of the discipline of the department. These kinds of restrictions are fairly easily accepted under most circumstances, but despite this Hagstrom sees them as "a particularly insidious form of the subversion of scientific norms", because new problems frequently cross disciplinary boundaries.

There is obviously, says Hagstrom, some tension between norms

of individualism and norms of interdependence. This is reduced by gift exchange which emphasises both the independence of each party, and the solidarity that exists between them. But this sort of relationship is not satisfactory when close co-operation is required.

There are various types of teamwork and collaboration: free collaboration without a division of labour; free collaboration with a division of labour; teams including students and technicians; complex teams in basic research.

10.56 The Growth of Specialties

10.561 Social Control

Hagstrom writes:

Colleague control is exercised within groups of specialists who share an interest in certain aspects of nature, communicate with one another more than with outsiders, and transmit their goals and skills to succeeding generations. There are many such communities in science, and the relations among them make up much of what can be called the "social structure" of science.

(Hagstrom :1965:159)

This is in contrast with the concerns of the Mertonian approach -- the norms of communality, disinterestedness, scepticism, and universalism. The type of social control that Hagstrom refers to above relates primarily to the types of knowledge being produced and transmitted, rather than with the mode of transmission.

In this context, how are the goals of specialties laid down?

Hagstrom writes:

The formal organization of a scientific discipline is responsible primarily for training recruits and maintaining channels of communication. Its most important units are university departments and scientific societies. Because disciplines in modern science tend to be large and heterogeneous, they cannot serve as informal communities in which recognition is sought for and achieved. Rather, each discipline is divided into smaller communities -- specialties -- consisting of scientists engaged in research along similar lines. (Hagstrom :1965:159)

After discussing the meaning of "similar" in this context (it refers primarily to ease of movement between different scientific tasks), he defines specialty:

... problems can be classified, and "specialty" will be used here to refer to a category of problems. Such categories are socially recognized: they are used in the organization of scientific meetings, journals, and teaching, and in advertising for jobs. Scientists identify themselves according to their specialties. (Hagstrom :1965:162)

He visualises a hierarchy of classifications, ranging in specificity from such terms as "physical sciences" or "chemistry" on the one hand, to terms such as "steroid chemist" on the other. He thinks of each sub class as having a real or potential social meaning, and suggests that although science has grown greatly in recent years, the size of the specialties may have remained the same, with maintenance of the same type of informal communication networks. He writes:

Even as communication in science occurs largely among members of the same specialty, recognition is usually awarded by colleagues in the specialty: the primary locus of social control in the sciences is the specialty. This means that, once a specialty becomes established, it tends to be self-sustaining. (Hagstrom :1965:163)

Despite this, the specialties naturally affect each other's growth.

Hagstrom is at his most interesting when considering the relationship between specialties inside a discipline. He mentions the hiring policies of departments, noting that the distribution of specialists may represent a compromise between specialties, and he notes that potentially disruptive intra-departmental competition is reduced if each department hires only one specialist in each area. Although there are forces working in both directions, on the whole the forces of dispersion are stronger than those of concentration.

10.562 Prestige of Specialties

He next considers the "hierarchy of the sciences" noting that

disciplines and specialties have different levels of prestige, both within the scientific community, and in the wider society. Although scientists will not normally talk in these terms, none the less, there is normally a wide measure of agreement about this hierarchy.

On criteria for awarding prestige, he writes:

Relations between individual scientists tend to be regulated by the exchange of information and recognition. Recognition is given for information, and the scientist who contributes much information to his colleagues is rewarded by them with high prestige. This process can be generalized to the relations between groups. (...) Information produced in one specialty or discipline may be utilized in another. Sometimes the exchange is symmetrical ... (but) usually, however, the relation is asymmetrical: information obtained in one specialty may be important in a second, but information produced in the latter may have few or no consequences for research in the former. When this is so, those in the former specialty may claim and be awarded higher prestige.

(Hagstrom :1965:168)

This is especially clear in physics where theory is well specified, but may be much less clear in areas such as biology, where theory is less well unified.

This information-recognition exchange system is not the only source of differential specialty prestige, however. Hagstrom also mentions the methods of investigation, suggesting that specialties with a higher proportion of theorists, or theoretical work, have higher prestige than those that are more empirical. There are a number of reasons for this. The best students are usually selected to do theoretical work, but the most important reason is as follows:

Theory controls empirical research, whereas empirical research provides conditions for the successful application and manipulation of theory. Thus, although the activities of theorists and experimenters are interdependent and the discoveries of each influence the activities of the other, a qualitative difference in the kind of influence results in differences of prestige. (Hagstrom :1965:172)

There are also other factors. He mentions, among these, the

practical results of the discipline, the prestige of instruments used, and the social base (meaning that if say, agricultural science, developed in low status agricultural schools, then it too, would tend to have low status.)

Hagstrom next examines some correlates of specialty prestige, particularly in relation to mobility of labour. Thus, the specialties with the highest prestige find it easy to recruit good students, and of course, within the specialty there is concentration of effort on high prestige problems. Cross-specialty mobility is low, but such of it as there is is mostly in a downwards direction.

10.563 Specialist Goals

Much of Hagstrom's discussion concerns the "goals" of a discipline or specialty. Thus, he writes:

The prestige-ranking of specialties is a collective manifestation of the award of recognition to individuals, and it has an analogous social-control function. An individual who pursues goals thought to be peripheral to the aims of his discipline may receive less recognition, and this will tend to reduce his motivations to deviate. A specialty -- a group, however loosely bound -- the goals of which deviate from the central goals of the discipline, will typically receive low prestige. This reduces its ability to recruit practitioners, inhibiting its growth. To grow and to receive a greater share of scientific positions, facilities, and honors, the apparently deviant specialty usually must demonstrate that pursuit of its distinctive goals contributes to the achievement of the central goals of the discipline. (Hagstrom :1965:176)

He goes on to consider the "orderly succession of goals", noting that discoveries generate new problems, and may therefore lead scientists to reconsider the relative importance of different problems, and thus lead them to pursue new goals.

Next he discusses fashion:

- (1) The prestige of a specialty is strongly affected by the uses nonspecialists within the discipline may make of its discoveries. ...
- (2) Specialties with high prestige tend to attract new workers.
- (3) Some scientists are attracted to

the high-prestige specialty, or use its results, not for any intrinsic reasons but because of their novelty, popularity, and the fact that the use of the results will impress others not familiar with them. (4) Specialists in other areas may condemn those who engage in the newly popular field as following fashions and assert that the field has been given unjustifiably high prestige. (5) The test of a fashion is the duration of the popularity of a field. A merely fashionable field will pose popularity after a short time. ...
 (Hagstrom :1965:184) ¹

The discussion of fashion leads Hagstrom on to talk about leadership -- leaders may develop a particular field through being emulated by followers. But for leadership to develop, two conditions must be met. Firstly, the followers must be able to change their fields easily, and secondly, the leader must be able to demonstrate his ability -- something which is easier in the formal sciences, and the mathematical aspects of the empirical sciences, than elsewhere. Where leadership is clear, it becomes possible for goals of specialties to succeed one another in a relatively orderly manner -- but this in turn, ofcourse, helps to identify leadership. Hagstrom notes, however, that the succession of goals in science is not always orderly, and there may be clash between goals of different specialties, with no general agreement about what constitute the criteria for judging relative importance. This situation manifests itself in the emergence of what Hagstrom calls "deviant" specialties -- those constituting "groups whose members feel they are not awarded as much prestige within the

1. The last proposition is open to some question; if the example of the inert gas compounds is considered, an initial serendipitous discovery opened up a new area, which was then entered by a number of workers who developed a theory to account for the previously anomalous phenomena. In a relatively short time this theory was developed, and found to be satisfactory, and the field became of much less "objective" interest.

discipline as their efforts deserve."

10.564 Deviant Specialties

There are two kinds of deviant specialties. One comprises those specialties with members who accept the goals of their discipline but believe their specialty is much more important relative to these goals than others give it credit for. The other comprises specialties with members who in effect reject the central goals of the larger discipline and, therefore, the legitimacy of the prestige system in it. For convenience, let us call the former specialists "reformers" and the latter "rebels". (Hagstrom :1965:187)

The prestige of the specialty depends on the contributions made to other specialties and disciplines, combined with an estimate of future likely contributions. There may be disagreements about the latter, and some specialists may feel that their specialty is underrated. These would be reform specialties. In the case of rebellious specialties, the specialists would agree that their goals are not the same as those of the discipline. In either case, of course, rewards and prestige are disputed, and this leads to conflict.

Dissensus works itself out in various ways at various levels of organisation. Thus, in the absence of an agreed prestige hierarchy of goals, decision making in organisations becomes more difficult. In university departments selection of new members can no longer be solely on the basis of excellence. Tenure problems may also become acute. The individual scientist may find that he faces a depressed job market. If a minority is well represented in a department it can act as a veto group, and a quota system of appointments can be adopted. In this manner, a few departments may become the territory of a particular deviant specialty. Other disputes arise over curricula, especially graduate curricula. One way out of this is to allow professors autonomy to determine their

own curricula. Hagstrom calls the sort of processes mentioned above primary adaptation.

Another area in which conflict typically results is that of the scientific societies and journals. There is competition between the specialties for space, and where there is general lack of goal consensus, the decisions of editors and referees will be called into question. Primary adaptation in this case consists in giving the representatives of deviant specialties places on journal committees, and in the formation of separate sections. This may lead to structural differentiation.

Thus Hagstrom mentions three areas in which primary adaptation may take place -- in the training of graduate students, the outlets for publication, and the allocation of university posts. They are "primary" because they do not involve structural change.

10.565 Differentiation

On occasions the deviant specialty is re-absorbed by the discipline, or dies out. On other occasions primary adaptation may only be but a step in the direction of disciplinary differentiation. Hagstrom writes:

Structural differentiation re-establishes social control. It begins with the organizational controls called into play when deviant specialties challenge the legitimacy of the informal organization of a discipline. It results in the formation of a new discipline with its own organizational controls -- university departments, scientific societies, and channels of communication. After differentiation takes place, the organizational controls are consistent with the prestige hierarchy of specialties in the discipline; as a result the controls of formal organisation are less likely to be used.
(Hagstrom :1965:208)

Differentiation is inhibited in a great many ways: deprecation of the importance of departmental affairs by many scientists; the

desire to avoid conflict; the fact that there may well be continued identification with the old discipline; the fact that there is no legitimating ideology for the new discipline; the fact that departmental structures are rigid; all these work against differentiation. Leadership of the right kind can be of great importance.

Hagstrom writes that:

Communication precedes community, and community precedes self-identification. Scientific publications devoted to a special field precede the emergence of the field as a discipline, and the emergence of the discipline precedes the identification of scientists with it. (Hagstrom :1965:210)

For this reason a new scientific periodical may emerge before the emergence of a new discipline. The primary reference group of a scientist constitutes those who read his work, and scientific recognition comes through the acceptance of papers for publication, and their approval and citation by the reading public.

10.566 Ideology and Utopia

Hagstrom writes:

Every established discipline possesses an ideology, a more or less explicit justification of its privileges and the claims it makes upon the scientific world and the larger society. These ideologies are partly alleged facts about the contributions of the discipline and partly evaluations about what is or should be considered "interesting" and "intrinsically important".
(Hagstrom :1965:211)

The ideology of a discipline delineates its area of jurisdiction, especially in relation to rival claims, and resists those who tend to regard the discipline as being of purely instrumental value. In addition it regulates relations between the specialties of the discipline. He writes that:

Corresponding to the ideologies of established disciplines are the utopias of newly emerging disciplines, justifications of proposed changes in the structure of science whereby the new

discipline will gain a more secure position. Disciplinary ideologies tend to be restricted in scope, oriented to specific audiences, and implicit, while disciplinary utopias tend to be "imperialistic", almost unrestricted in scope, oriented to very general audiences, and explicit. (Hagstrom :1965:213)

Utopias are, in fact, frequently addressed to lay groups.

Emerging disciplines are frequently in uncommunicating schools, and in the utopia their common features are emphasised.

10.567 Purification

Emerging disciplines, Hagstrom suggests, are "inherently heterogeneous", because there is typically a lack of common training and scientific experience. Furthermore, the new discipline cannot restrict its membership, since support has to be sought from many quarters. Men whose interests are purely theoretical are brought into contact with those who have applied, or both pure and applied interests.

After differentiation, then, a final process is required -- that of purification -- in which only those whose interests are defined as being pure are allowed to remain in the university structure; separate professional societies for those with pure and applied interests may be formed. It is at this stage that the disciplinary utopia is transformed into an ideology, and the more expansive claims are abandoned. The belief system begins to protect and support the status quo -- the existence of the new discipline. Once again Hagstrom emphasises the importance of leadership in the process of disciplinary differentiation.

10.57 Anomie

Essentially, Hagstrom sees the process of social and cultural change in the following way: segmentation begins with cultural change -- the development of new goals in the scientific community;

scientists tend to disperse themselves over the range of possible problems, and do so to reduce the degree of competition; this leads to less social and cultural cross-fertilisation and contact, and increased dispersion results. Those who are central to the discipline may attempt to use formal sanctions, and then overt hostility may arise. Goals and standards are questioned. Under these circumstances primary adjustment may work, but if it does not, then formal differentiation may follow. This process requires the existence of special channels of communication, the formation of a disciplinary utopia, and the presence of leadership. In organisations, formal groups such as units may first be set up, and then departments may follow. Hagstrom writes:

Disciplinary differentiation involves the specialization of individual scientists and the segmentation of disciplines. These complementary processes usually lead to the integration of scientists in disciplines, but under some conditions they need not have this consequence. If a branch of science is characterized by a general absence of the award of recognition, or the scientists in a specialty with low prestige believe they cannot feasibly change specialties, then recognition will cease to have its typical meaning as an incentive. The behaviour of scientists will not be regulated in the way suggested here, and the specialties in a discipline may have no orderly relations with one another. When this happens, the branch of science can be said to have an anomic division of labour.
(Hagstrom :1965:226)

Anomy is thus a situation where there is an absence of strong norms. Hagstrom suggests that there is anomy in mathematics -- there is a general absence of opportunities to achieve recognition, and there is also an absence of accepted criteria for ranking specialties in mathematics according to importance. The consequences of this state of anomy are several. Firstly, mathematicians frequently stress the importance of their own work. Secondly, ritualist, retreatist, and rebellious actions becomes more common.

10.58 Functional Differentiation

Another type of structural change is that of functional differentiation. This arises when there is a substantial amount of cross-disciplinary collaboration and consultation, and is, Hagstrom suggests, rather rare in science. The best known example is that of theoretical and experimental physics. The two main conditions for the growth of such functional differentiation are (a) the fact that logical elaboration of abstract theory requires considerable specialised training, and (b) the fact that data collection has become increasingly dependent on great technological sophistication. In this way, the two groups are inter-dependent.

10.59 Disputes

Hagstrom opens a discussion on the conduct of disputes by examining the development of "higher order social norms". Thus, he writes:

In the course of disciplinary differentiation, ideological differences sometimes lead to disputes between scientists about the merits of different goals. These disputes are symptomatic of social strains and are usually resolved when differentiation is completed. The claims of each of the opposing parties may eventually become valid and acceptable to the other. When the groups have become differentiated, both parties may adhere to their original goals and standards, but it will no longer be felt that they contradict each other. Consequently, segmentation and functional differentiation are examples of logical evolution; higher order social norms (the norms of science) are specified and differentiated for lower order structures. (Hagstrom :1965:254)

This is a passage in which Hagstrom clearly locates the norms of science in the knowledge. He contrasts it with a process that he calls "dialectical evolution", where different and competing competing approaches to the same material are presented. In this case it is not possible to resolve the dispute by means of social differentiation, and one or other of the approaches must be wrong,

and will have to be abandoned. Hagstrom notes that:

From a slightly different point of view, the existence of opposing schools of thought reveals a possible strain between two central sets of norms in science. There are, first, norms giving the individual scientist liberty to accept or reject alternative approaches. The other norms provide that recognition and evaluation of scientists, even their right to be considered as scientists, should depend on competence and excellence. The problem is to apply this second set of norms without compromising the first. (Hagstrom :1965:254)

In conformity with what Hagstrom calls the "positivist ideal", few scientists admit to the existence of "schools", and argue that there is no reason to become intensely involved in disputes. None the less, they do not act like this. The positivist ideal is most applicable when five conditions are met. These are (1) when disagreement is of strictly limited intellectual scope, when (2) it does not involve major differences in research programmes (3) when it is easy to make decisions about disagreements, (4) when the degree of implication for textbook education is low, and when (5) there is, overall, a general consensus throughout the discipline.

He discusses types of disagreements, and here he is heavily dependent on Kuhn's approach. He mentions the case of scientific revolution, noting that it may be difficult to know whether to decide for or against a revolutionary solution, since its immediate superiority may not be clear. Other types of disagreements may arise through less fundamental theoretical innovations, or through the discoveries of paradoxes in the formal sciences. Other, vaguer types of disagreement arise when different schools grow up, with arguments over methods or "style".

Next, Hagstrom introduces the notion of alienation, noting that substantive disagreements do not usually result in the alienation of scientists from each other. Disputes may be translated into

arguments about technical competence or priority. Once alienation starts, however, it tends to spread. Opponents may feel that their contributions are not recognised because of the conclusions advanced, and not because of the methods. Affirmation is then sought amongst those who are in agreement, and opposite schools form which results in more difficult and less frequent communication. In this sort of situation there is frequently abuse of power, scientists tend to think in terms of gaining power, and appeals are made to non-scientific audiences.

Both goal conflict and substantive disputes are characterised by withholding recognition. Decisions by scientific authority are arbitrary, and appeals are made to outside audiences. In attempts to control controversy, scientists may minimise disputes and argue that there are no fundamental disagreements -- that theories are convenient fictions, that disputes do not exist, or that if they do, they are not really scientific. Alternatively, if the disputes do concern science, they are not about truths, but about techniques or tastes. Scientists tend to be permissive in these sorts of situations, suspending judgement where possible.

Other methods for controlling controversy are more exclusively social. Polemics may be suppressed at meetings, and refused by the journals. Expressions of controversy may be restricted to an elite, and to special occasions. There are certain dysfunctional consequences to these modes of control of controversy. Some scientists may remain unaware of facts that would be useful to them in their research, and this may lead to poor allocation of research effort between problems.

Next Hagstrom discusses the resolution of conflict. Contro-

versies are usually short, and are resolved one way or the other by new discoveries. Though few scientists recant in public, and many do not change their views, the balance of opinion in the scientific community will alter as old scientists retire, and young ones with different viewpoints come to take their place.

10.510 Conclusion

Hagstrom's approach to the sociology of academic science is very important. It includes a wealth of empirical material, and some of his insights, particularly about informal social control, are very important. It is unfortunate that he does not succeed in coming to terms fully with the Kuhnian insight, although in fact he utilises it on frequent occasions. Thus, he starts off from a Mertonian point of view, and never quite spells out the logic of the notion that the locus of social control in science lies in the specialty. The logic of this notion is that knowledge is itself normative, but Hagstrom never quite succeeds in recognising this fact, and reorganising his approach around this insight.

Despite this fact, his book is one of the most important recent contributions from the Mertonian tradition. Part of its value lies in its general lack of dogmatism. He deals with much empirical data, but the organisation of this data is not highly determined. At times this makes the book a little difficult to read and follow.

One aspect of Hagstrom's work that has not been used in this thesis is his discussion of disciplinary structures. The logic of the main inquiry led straightway to specialties, without a discussion of disciplinary systems of social control, including notions such as accommodation. This is obviously important, however, and Hagstrom,

perhaps because of the structure of his study, which was not concentrated on a single specialty, has chosen to write extensively about it. At some time this line of inquiry must be further developed.

10.6 A Further Brief Survey

The authors above have been selected because of the use that has been made of them in the work covered by this thesis. In the section that follows the work of several other authors, who might be considered relevant, but whose work has not been extensively used, will be mentioned.

10.61 Ben David

Ben David's contribution to the sociology of science can be seen in one respect, as the spelling out of the implications of notions of competition between scientists. These notions of "role hybridisation" have been used (Ben David and Collins :1966; Ben David :1960) to explain certain sorts of innovation. In the former paper, Ben David examined the German universities in the nineteenth century, and in particular promotion chances in certain established scientific disciplines, and noted that, because of blocked promotion ladders, there was strong pressure to innovate, and open up new areas of science. This part of the argument is similar to that used by Mulkey and Turner (:1971). The notion of role hybridisation does not merely involve innovation, however. It involves, as well as the bringing together of different ideas, the bringing together of different aspects of two roles, and the fusion of those aspects into a single new role. This occurred, in the case of scientific psychology, in nineteenth century Germany; physiology, a high prestige discipline, offered virtually no chances of promotion.

Philosophy was lower prestige, but offered much better chances of promotion. There was an incentive, therefore, for students trained in physiology, to improve their career chances by moving into philosophy. To do so, however, meant losing status, since philosophy was much lower status than physiology. To minimize the loss of status, the mobile scientists accepted part of the subject matter of speculative philosophy -- the manner in which the mind worked -- but imported techniques and approaches used in physiology -- the "scientific method". Hence, through role hybridisation, a new discipline was born. Unfortunately, this paper is somewhat marred by the fact that only one of the psychologists mentioned (Wundt) moved in the manner suggested. The other early practitioners, although less important than Wundt, were all philosophers.

In an earlier paper (:1960) the term role hybridisation was used in a different context. Here, the roles being hybridised were, on the one hand, academic roles, and on the other hand, practical or problem solving roles. The combination of these two roles was seen as leading to important innovation. The two cases he discussed were bacteriology, and psychoanalysis.

In general, Ben David stresses the importance of establishing situations under which a scientific tradition can be established, and he indicates that the development of appropriate scientific knowledge is dependent on the establishment of an appropriate social role -- one where an end product of the role is the production of knowledge, and where there are students ready to carry on the tradition.

The notions of competition in science have been further spelled out by Collins (:1968).

10.62 Downey

Downey has also used the sociology of science as an area in which to demonstrate more general sociological concerns. His argument proposes that organic models have increasingly come to dominate in sociological theory, and that mechanical models, in comparison, have not been fully exploited and developed. Arguing that organic models are inadequate in science, he develops a mechanical model of the scientific community, which while satisfactory in some respects, would appear to be somewhat strange in others. In particular, his insistence that disciplinary segmentation is an example of mechanical division of labour because after segmentation scientists are essentially doing the same thing, would appear to be very misconceived. (Downey :1969)

10.63 Clark

Clark has discussed the institutionalisation of innovations in higher education (Clark :1968), outlining four models whereby cultural elements are seen as being adopted by actors:

1. An organic growth model.
2. A differentiation model.
3. A diffusion model.

4. A model that he himself constructs called the combined process model. Inside the university structure the organic process model is seen as being the most relevant. The diffusion type model is more important in studying innovations that develop outside the university structure, or those that diffuse into these structures. Hence some combination is required.

10.64 Jenkins and Velody

These authors have developed what they call a "dimensional

model" for the understanding of the institutionalisation of interdisciplinary fields and non-conventional activities. In this model they have sought to minimise rigidity and set developments in a wider social context, to avoid premature prescription of empirically open points, and to reject models that strayed too far away from substantive material. (Jenkins and Velody :1960; 1971)

The model which they develop identifies four dimensions which have to be examined if a non-conventional activity is to be understood -- the problem, its immediate setting, its materials, and its actors. Although it draws attention to certain points that are of importance, it has yet to be shown that it has any utility over and above this. The model produces a breakdown of action that is rather far from commonsense, and although this is not, of course, a criticism in itself, it none the less requires empirical illustration and validation. This has not yet been provided.

10.65 Whitley

Whitley has been the most prolific -- indeed virtually the only -- British contributor to the literature on citation networks, and the uses of citation indices. In this work he has covered the cases of animal physiology (:1969) British sociology (:1968a), and more generally, British social science (:1969a?). More recently he has concentrated on the role of journals in controlling the formal communication aspects of a discipline and specialty (:1969b). His most recent work has concentrated on Price's notion of the invisible college, and he has been concerned, like Crane and Mullins, to determine whether invisible colleges in particular, or specialties in general, can be identified through citation and other interaction networks. In the case of animal physiology, some sort

of invisible college was identified, but in the case of British social science, no such invisible college was discovered.

10.66 Crane

From the point of view of the theoretical perspective developed in this thesis, some of the most interesting work to come out of the network analysis tradition has been carried out by Crane. The first study that she carried out was on a group of sociologists -- those who had studied the spread of innovations in a rural area (:1969). She felt, as a result of this study, that Price's notion of the invisible college might not be the most appropriate way of looking at social organisation in an academic discipline. Instead, she used the notion of a "social circle" (Kadushin :1966 and Znaniecki :1965), finding nothing so clear as is implied in the notion of invisible college. Given that there is a "seamless web" of interactions across the whole face of science, then she found that one group became isolated from other groups only when certain scientists developed a position of leadership in a particular field, and asserted its independence.

11 A THEORETICAL APPROACH TO SCIENTIFIC GROWTH

This work has now reached a point where some implications for a theoretical approach may be seen. Cultural elements that concern crystallographic methods and their proper use have been illustrated in the early part of this thesis. The fact that the workers were also in communication with each other has also been illustrated. For these two main reasons, crystallography is defined as a scientific specialty.

In the history of British X-ray crystallography, various important advances were mentioned or discussed. Some of these achieved exemplary status in the community. There were clearly defined logical and algebraic statements about the relations between reflected rays and crystal structures. In addition, there were ideas, like the one developed by the Braggs, that crystal planes "reflected" X-rays. It is suggested that these three elements comprise three aspects of what Kuhn has called a disciplinary matrix -- exemplars, symbolic generalisations, and models. For this reason, these terms, together with the notion of "exemplar set" and "specialist matrix" are used in the discussion. The exemplar set refers to that group of exemplars used by workers in a specialty at a particular time, or alternatively, that group of exemplars used by workers in a specialty over time. The specialist matrix is like the Kuhnian disciplinary matrix, except that it refers to shared elements in a specialty rather than in a discipline.

Using these terms, it becomes clear that X-ray crystallography is a rather unusual kind of specialty. Its main exemplary achieve-

ments tend to relate to either (a) the development of the X-ray crystallographic method, or (b) to the solution of difficult crystal structures. The workers in the specialty are deeply concerned about the use and development of the technique. For this main reason X-ray crystallography is defined as an example of a technique based specialty -- one where the specialist matrix and exemplar set relate primarily to the development of methods. Many German X-ray crystallographers, unlike their British counterparts, however, appear to have been preoccupied not so much with the technique of X-ray crystallography itself, but on the light that it might cast on basic physical problems. In many instances, when X-ray crystallography became less relevant to physical theory, it was no longer used. It is suggested, therefore, that German X-ray crystallographers were members of a theory based specialty -- a specialty where the specialist matrix and exemplar set relate primarily to the development and exploitation of theory.

Finally, another possibility, illustrated in part by the phage group of molecular biologists, is explored. This constitutes a situation where there were no well developed exemplary applications or symbolic generalisations to guide scientific action. Such guides as there were gave only a general indication of appropriate actions. Yet, in some respects the phage group appeared to constitute a specialty in that there were interacting groups of workers, at a time when this cultural achievement was still very limited. For this reason, it is provisionally defined as an example of a problem based specialty -- that is, a specialty which possesses no well defined exemplar set or specialist matrix, but constitutes an interacting group of workers who believe themselves

to be concerned with the same, or connected problems. The way in which specialties develop -- does the success precede to social network, or vice versa -- thus becomes a matter for empirical investigation.

In British X-ray crystallography, members of the specialty who misused the techniques were the objects of strong negative sanctioning. This, and the fact that there was so little misuse of methods indicates that there were very strong standards relating to the use of methods. On the other hand, many different types of crystals were simultaneously studied by members of the community, who also had a variety of different attitudes to the work on proteins. This indicates that standards that related to areas of work were weaker than those concerning the use of methods.

For this reason, a distinction between permissible and impermissible work on the one hand, and preferred and non preferred work on the other, is made, and it is suggested that in technique based specialties where the exemplar set concerns first and foremost the methods, that the permissible -- impermissible distinction relates to the methods. The preferred and non preferred standards, which are less strong, arise partly from the methodological standards, partly from a vision of the future development of the specialty, and partly from demands made on the actor from outside the specialty. Since the question behind this work is -- what is it that determines the direction of cultural change in science? -- it is clear that all these factors must be distinguished, and the differences in the mechanisms affecting permissible -- impermissible, and preferred -- non preferred must be established.

In this work on X-ray crystallography, the use of the Mertonian

norms of science has been avoided. This is for two main reasons. Firstly, Merton's norms are general, relate to the process of knowledge handling rather than to knowledge itself, and in any case, divorced from a positivist world view do not offer any proper guide to action. Secondly, and more generally, the term 'norm' has been avoided, since it was found easier and more appropriate to describe the standards of the community of X-ray crystallographers in terms of the Kuhnian vocabulary used above.

The plan of this chapter, unlike this summary, is to work from sociological issues raised in the literature review to the theoretical scheme outlined above. At appropriate points it is illustrated with reference to the data on X-ray crystallography.

11.1 Critical Points from the Literature Review

In the literature review certain points have arisen with some regularity. Some are of direct relevance to the present study; they will be reviewed in what follows.

1. There is concern about the relationship between formal disciplinary structures, informal communication patterns, and the structures of knowledge. This problem has been raised explicitly or implicitly by Hagstrom, Kuhn, Mullins, Fisher, Crane and others. Writers in the Mertonian tradition have not, in general, written extensively on the actual content of scientific knowledge; their concerns have been different.

2. As a specific example of this there is the question, primarily one of network theory, as to whether specialties can be discovered by examining networks of interactions. Is science an "undifferentiated seamless web", or is it divided into specialties

which have some existence at a network level? Writers such as Mullins, Crane and Whitley have been concerned with this issue, and although the outcome of the debate is by no means clear, it seems probable that new specialties should be visible as high density groupings in interaction networks, if appropriate indicators of interaction are used.

3. Another, and related problem, concerns scientific identities and disciplinary and specialist labels. It is clear from the work of Fisher that these do not simply relate to aggregates of skills not found elsewhere. Identities and labels have a social meaning, and their relationship to skills, while undeniable, is complex.

4. Another area of discussion concerns the nature of social control in science. The recent debate for and against the Mertonian position has already been discussed, and the proposals put forward by Kuhn and some of his sociological interpreters have been presented. A second, and related debate, concerns the nature of the Kuhnian exemplars -- are they a special case of norms, or not?

5. Other authors have asked where new knowledge comes from. What are the sources of innovation? This debate has tended to take place on two fronts. Firstly, there has been interest in the structural situations that favour innovation (Mulkay, Ben-David), and secondly there has been an interest in the way in which knowledge as such is actually developed (Kuhn).

6 Hagstrom has written extensively about the structural processes involved in disciplinary differentiation and the growth of new specialties. He is one of the few authors who has attempted to characterise the relationships between neighbouring disciplines and specialties.

Points (1) and (6) will not be discussed further in this chapter, as they are either too general, or are outwith the scope of the theoretical discussion. Point (5) will be discussed, although in rather different terms -- the question asked will be, what is it that affects the direction of scientific growth? Points (3) and (4) will be discussed in some detail. This leaves point (2) -- the question of the discrete existence of specialties at a network level. For the purposes of this study, specialties have been assumed to exist in this way; here the work lies on the authority of the existing literature.

11.2 Basic Assumptions

11.21 Natural Science as an Institution

It is assumed that natural science can be characterised as a social institution, that is as a cluster of actions, spatially and temporally distributed, identifiable by actors and sociologists as specifically scientific, and associated exclusively with a set of fully differentiated scientific roles. The definition of a social institution would normally, in part, refer to "norms" -- rules that are explicitly or implicitly held by the relevant actors, which govern their actions; however, in this case, for reasons that will become apparent during further discussion of the work of Kuhn and Mulkay, the term "norm" will not be used, and terms such as "exemplar," and "specialist matrix" will be employed -- terms that avoid the unacceptable implications of some of the uses of the term "norm". This should not be seen as altering, in any important sense, the meaning of the term "institution".

11.211 Merton's view of Science

Merton was the first sociologist to recognise that science

might be seen as an institution. His four norms characterise aspects of action that do not depend on the specific scientific work being undertaken. They refer rather to the process of handling and transmitting knowledge. If followed, they would, in Merton's view, lead to the accumulation of well reasoned knowledge, and the rejection of badly argued or prejudiced contributions.

11.212 Criticism of Merton's View of Science

As was seen in the literature review, Merton's scheme has come under considerable attack in recent years. His approach rests on certain assumptions that have themselves come under attack. The most important of these concerns the process of scientific change, which Merton sees as being essentially cumulative. He appears to have an image of a stockpile of certified scientific knowledge, and his norms constitute the filter which stops incorrect knowledge joining that stockpile. It is this cumulative view of science, which is certainly very widespread, and appears to be consonant with positivist philosophies of science, as well as with what scientists themselves typically say, which has been under attack for example from Kuhn. Merton, who is of course a functionalist, saw his norms as being functional to the development of science and the growth of scientific knowledge. However, others have since brought aspects of science that were previously reserved for philosophers into the sociological arena. Kuhn, for example, although trained in a tradition which accepted the distinction between the context of discovery and the context of justification, no longer finds it easy to make the distinction between the two, which is necessary to the positivist or empiricist viewpoint underlying Merton's work; as Dolby has noted:

Writers such as N.Hanson, P.K.Feyerabend, S.Toulmin and Kuhn have argued that theoretical and philosophical factors are presupposed in every aspect of scientific inquiry. Scientific method, as it is actually and inevitably carried out, loses its character of a logically straightforward process, once it is realized that such factors are presupposed in the meanings of the observational and theoretical terms, in the characterization of the problems tackled by a science, and in what is to count as a solutions to those problems. (Dolby :1971:9)

Thus the nature of the knowledge "filter" mentioned above is problematic, and many no longer judge Merton's clear approach to be sufficient.¹

So, although, as Mulkay has pointed out (Mulkay :1969), the Mertonian norms constitute a case where functionalism has apparently succeeded in accounting for an institution in social change, the change described is one which (a) does not involve the norms themselves (Mulkay), and (b) is no longer considered by its critics to be a valid account of the process of cultural change.

Further problems have arisen in the Mertonian position. There have been conflicting reports about the empirical status of the norms, and other workers have suggested that they are characteristic of academic life in general, rather than of science as such.²

While there has probably been an overreaction to the Mertonian view of science in some quarters, there is none the less need for substantial revision of the norms, and the attendant description of the institution of academic science. In passing on to further discussion, however, the nature of the debt owed to Merton should

1. This is a facet of the argument recently developed by Barnes and others (Barnes :1971) who argue that sociological explanation is as much required in the case of the supposedly rational, as it is in the case of the irrational. This has not, in the past, been accepted by many workers in the Mertonian school -- see Cole :1970, for example.

2 However, the rival approach developed by Kuhn has had less than full success in offering criteria of demarcation.

be made clear. Firstly, he developed a theory about the channelling of motivation into specific kinds of action -- the relationship between offering certified knowledge, and the achievement of recognition -- and he illustrated this thesis with reference to priority disputes. Secondly, he characterised the norms, which although now under question in the manner described above, first opened up the area to the sociology of science. It is for this last achievement that workers in the area are strongly indebted to Merton.

11.22 The Norms and Standards of Natural Science

The development of an alternative approach to that advocated by Merton has had to wait for the work of T.S.Kuhn.¹ This work has been described in some detail in the literature review, and will be further discussed in what follows. Essentially, however, Kuhn goes to the knowledge, theories and techniques of science, and locates the standards of acceptable scientific action there. Thus, workers such as Mulkey and Barnes and Dolby have argued that the paradigm (or disciplinary matrix) provides the basis of scientific social control. In its broadest sense, then, this constitutes the second fundamental assumption in this work.

Despite the fact that Kuhn is not a sociologist, and has only recently begun to link up his work to the body of sociological literature, this approach is especially attractive to the sociologist, as it involves many of the elements of a sociological explanation. Thus, the paradigm is a 'received achievement' which is

1. Kuhn's work comes from a philosophical tradition that has been developed by writers such as Hanson and Toulmin, as well as Kuhn himself. Rather than discuss the separate approaches of these philosophers, Kuhn's writing alone is considered.

accepted by a group of workers and it guides their research actions. Deviance is not normally permissible, and Kuhn implies that deviant action will be answered by negative sanctioning from other members of the group.

Kuhn's approach differs from that of Merton in a number of important respects. The most obvious contradiction is that Kuhn argues, essentially, that scientists are normally dogmatic, clinging to central theories and approaches, and ruling out radical innovation. Merton argued that scientists are open minded, and should treat truth claims sceptically and fairly, judging each on its "merits". "Merits", in the Mertonian approach, are unambiguous and relate to a positivist world view, while a Kuhnian approach would argue that work normally has merits only in so far as it conformed to expectations about pre-existing methodological and theoretical standards.

11.23 The Development of a Specialised Vocabulary

This chapter makes use of a number of terms, some of which are familiar in sociological language, and some of which, coming directly from the work of Kuhn, are not.

11.231 Specialty

This is a term that is used by Hagstrom, and it refers to a community of scientists who are engaged on work which is along sufficiently similar lines that they are able to judge the merits of each other's contributions. The members of the specialty are thus primarily responsible for awarding or withholding recognition. As Hagstrom puts it, "the primary locus of social control in the sciences is the specialty".

This idea has also been used by Kuhn, Mullins, Crane, and a number of other workers. In his most recent work Kuhn suggests

(with reference to the other two workers mentioned above) that it should be possible to locate interacting groups of workers who constitute scientific communities and share disciplinary matrices, without any prior reference to the fact that they share similar cultural orientations. This is an empirical assertion that has been reasonably well substantiated¹, and the result is that specialties should be distinguishable on both cultural and interaction grounds. In this view, then, specialties would be visible as (1) denser sections of interaction networks in that network which covers the face of science, and (2) clusters of scientific, theoretical and technical orientations however conceptualised.

In the work that follows it is assumed that X-ray crystallography constitutes a specialty in both of these senses. While no data is offered concerning interaction networks, evidence has been given, and will be further discussed, which shows that X-ray crystallography constituted a set of coherent cultural orientations, which were held by a continuous group of workers, who interacted, and awarded or withheld recognition from each other.

11.232 Further Sociological Vocabulary

1. Utopia. This term is used. It is defined in the sense employed by Mannheim.
2. Identity. This term is used to refer to the actor's perceived scientific status -- that is the 'label' which he attaches

1. Although there is still some doubt. Thus Mullins, Crane and Whitley identified relatively dense interaction networks in the areas of phage group molecular biology, sociologists working on innovation in rural science, and animal physiology, respectively, though they chose to conceptualise these in different ways. Mullins and Whitley discovered little such clustering in the biological sciences and British sociology, respectively. Although Price (:1963) has long advocated the notion of the 'invisible college', the relationship between the network analyses and Kuhn's work has come under attack from the philosopher, Musgrave (:1971).

to himself.

11.233 Non-Sociological Vocabulary

The further vocabulary used in this chapter is non-sociological, and for this reason is explained at somewhat greater length.

1. Specialist Matrix: the notion of the specialist matrix refers to "clusters of technical and scientific orientations" that are characteristic of the specialty. This is similar to the notion of disciplinary matrix that has been developed by Kuhn, except for one small and obvious difference. If the locus of social control is in fact located in the specialty, then it is to the specialty that we must look for shared orientations. While there may be shared orientations over the whole of a discipline, and on occasions these may be important, it is none the less in the individual specialties that we must look for the best specified scientific and technical orientations. For this reason the term specialist matrix is used; it is a matrix because it refers to a criss crossing set of orientations and cognitions that while being 'looser' than an exhaustive set of rules, is none the less well ordered, each part bearing a definite and coherent relationship to every other part.

The specialist matrix is thus similar both to what Kuhn previously called a paradigm, and to what Mulkay wishes to call cognitive and technical norms. Discussion of both of these points will be postponed.

The disciplinary matrix contains four elements, and these terms will be used in the theoretical discussion. They are:

1. Symbolic generalisations. These are generalisations that can easily be cast into algebraic form, which can be employed

without dissent by members of the community. In the case of X-ray crystallography, expressions such as Bragg's Law constitute examples of symbolic generalisations.

2. Models. These are general beliefs about the natures of the systems that are being investigated, and range, in Kuhn's definition, from the heuristical to the ontological. In the case of X-ray crystallography, a model at the ontological end of the scale would have been the actor's view of the nature of the atom -- as surrounded by an electron cloud of varying density. A model at the heuristic end of the scale would have been the notion that there were crystal "planes" that "reflected" X-rays.

3. Values. These are more generally and widely shared than the above, and relate to predictions, the relative worth of quantitative as opposed to qualitative data, and so on. An example of value disagreement in X-ray crystallography is the case of Bernal's and W.H.Bragg's different attitudes to the use of reciprocal space as a method of calculating structures from diffraction patterns. W.H.Bragg took the view that this method postulated constructs that were unreal, and hence to be avoided in preference to a more realistic mathematical account of what went on in the crystal. Bernal took another view -- that the simplicity and ease of the reciprocal space construct more than compensated for any loss in reality (Lonsdale :1962b:412)

4. The most important element in the disciplinary matrix is the exemplar. Kuhn writes:

By (exemplar) I mean initially, the concrete problem-solutions that students encounter from the start of their scientific education, whether in laboratories, on examinations, or at the ends of chapters in science texts. To these shared examples should, however, be added at least some of the technical

problem-solutions found in the periodical literature that scientists encounter during their post-educational research careers and that also show them by example how their job is to be done. (Kuhn :1970a:187)

Thus, in the course of his training the scientist is socialised into a whole set of procedures and applications, both methodological and theoretical. He does not simply learn formulae, or formal law statements, but he also learns how to manipulate them, and how to apply them to new problems that arise. The process of manipulation depends on the exemplary component of the specialist matrix. Symbolic generalisations have little meaning in the abstract -- only when they are tied to applications do they have clear implications for action.

There is a further important aspect of exemplar. Kuhn has suggested that the exemplar concerns the development of perceived similarity relationships in the stimulus to sensations route -- one step before interpretation in any conscious sense is involved. He wishes to deny the similarity between the learning in the stimulus to sensation route, and that involved in constructing theories on sensations. Thus:

One of the fundamental techniques by which members of a group ... learn to see the same things when confronted with the same stimuli is by being shown examples of situations that their predecessors in the group have already learned to see as like each other and as different from other sorts of situations.

(Kuhn :1970a:193)

He also notes that there is:

no reason to suppose that our neural apparatus is programmed to operate the same way in interpretation as in perception or in either as in the beating of our hearts. What I have been opposing in this book is therefore the attempt, traditional since Descartes but not before, to analyze perception as an interpretive process, as an unconscious version of what we do after we have perceived. (Kuhn :1970a:195)

He notes that the neural processes transforming stimuli to

sensations are learned by example, are transmitted through education, are more satisfactory than their rivals, and are capable of being altered if problems arise, or as a result of further education.

Consider, for example, the process of learning to drive a car. Although many, if not all, of the operations can and have been written down, in practice the only way to learn to drive is to drive -- perhaps to emulate an example -- and to practice until the skills involved are, for the most part, no longer conscious. One does not learn the appropriate time to brake by learning a set of stopping distances at different speeds. At best such a list of distances suggests to the learner that caution is necessary. One learns to apply the appropriate brake pressure at appropriate speeds, distances, weather and car conditions, by practice. Although some people write about their experiences there are many who would be unable to give a full and accurate description of their driving action, and yet who can drive a car perfectly satisfactorily.¹

This is perhaps the most important and least understood aspect of Kuhn's thesis. The operation of a "programme" which turns stimuli into sensations, a programme which all actors have, cannot be understood in terms of interpretation. It is there, he suggests, prior to the formulation of rules, and it is learned by direct experience, and not necessarily mediated fully through linguistic codes.² In this aspect of his work, Kuhn is clearly very

1. Compare this with Polanyi's description of the knowledge involved in riding a bicycle (Polanyi :1958:88).

2. There is an obvious difficulty here which has not yet been explored by Kuhn and cannot be discussed here. The difficulty lies in the fact that many of the exemplars come to scientists

dependent on the work of Wittgenstein in Philosophical Investigations.¹

Kuhn seems to be implying that a programme is developed during the process of scientific training that leads to cognitive standards that distinguish between like and unlike. Further, he also argues that even processes of much more conscious interpretation are learned at least in part through exemplary applications.²

All this vocabulary will be used and developed in what follows. Certain problems concerning Kuhn's use of the term paradigm, the global implications of scientific change involved in the adoption of such a scheme, and the relationship between exemplars and norms will be considered during the course of this exposition.

at least partially mediated through language, and hence have been codified and removed from their direct exemplary context. Textbooks, papers, descriptions of experiments, all of these have undergone this translation process. However, there is still a case for arguing that textbooks, papers, etc., do not, by themselves, constitute a scientific education -- it is through the direct experience and confrontation with experimental situations and necessary manipulations alone, that a student can be turned into a professional.

Thus, the fact that the author has read textbooks on X-ray crystallography does not mean that he is actually an X-ray crystallographer. It would be necessary to carry out practical training in the laboratory, learning rights from wrongs, before he could effectively do the work, and make the necessary cognitive distinctions.

1. Wittgenstein wishes to argue that in using the term "game" one is not committing oneself to a concept that is completely rule bounded. Whatever defining characteristic is isolated, he suggests that there will always be a game that does not share this characteristic. He writes that:

we see a complicated network of similarities overlapping and criss-crossing: sometimes overall similarities, sometimes similarities of detail.

... I can think of no better expression to characterize these similarities than "family resemblances"; ... And I shall say: 'games' form a family. (Wittgenstein :1968:32)

He stresses that the word "game" is used, in a context, and not defined beforehand.

2. There are similarities between these and an approach to

11.3 The Concept of Exemplar

The rest of this chapter revolves, in large part, around the development of a concept that has already been defined -- that of exemplar. This concept will be developed and applied to certain problems -- those that have been the main focus of interest during the writing of this thesis. The main problem, and one that will be approached from a number of different directions at the same time, concerns the direction of scientific growth. In Kuhnian terms the question can be expressed by asking: what is it that causes practitioners in a specialty to articulate on part of their paradigm rather than another?

11.31 The Exemplar Set

It is clear that one would expect the specialist matrix to change over time. New exemplars will be added, old ones will be dropped from use, values and symbolic generalisations will change in form, and models, particularly of the heuristical variety, may fall into disuse. When many or all of these processes occur in a radical form at one time, then the situation resembles what Kuhn has called a scientific revolution. However, even during times of normal science, there will be change in the components of a specialist matrix.

This process of change might be described as follows. At time A the student is socialised into the specialist matrix which contains a set of exemplars. These exemplars are taught through

computer problem solving using "heuristic" instead of simply algorithmic programmes, that has been developed by Simon (:1969) and others during recent years. A heuristic programme is one that includes "rules of thumb", which suggest on the basis of past experience, which decisions are likely to lead to successful solution. The past experience is either used directly, or it is transferred analogically from a similar problem solution.

textbooks and postgraduate monographs. In some cases they appear in the journals where they take the form of important journal articles that are emulated, and used as examples. The exemplars are also learned by direct modelling and emulation in laboratory work, at both an undergraduate, postgraduate, and post doctoral level. With a set of exemplars, the young scientist starts his career and is confronted with certain problems that are accepted as being problems by the whole specialty. These problems 'demand' articulation of existing exemplary applications. Some of these problems are soluble without great difficulty, but others involve substantial remodelling of symbolic generalisations, with the development of new exemplary applications. Thus there arrives a time B, when work is carried out in the same tradition as that at time A, but when it is guided by a subtly different set of exemplars. In other words, scientific action is no longer structured in the same way in all respects, and there may, in addition (since symbolic generalisations have a definitional function), have been meaning change. Clearly there may be greater or lesser differences in any tradition between time A and time B.

Another feature of this change over time, is that at different times and to different people, different problems become important. Exemplars may, in other words, be developed in different directions, and divergences may result in this respect.

It is this continuous process, the construction and abandonment of exemplars, that is most characteristic of the process that Kuhn describes as normal science, although there are elements in the above account that Kuhn might not find acceptable.

The term exemplar set has been used in the above passage, and

it will now be discussed. It refers both to that set of exemplars that the actors in a specialty refer to at a particular point in time in their work, and also to that set of exemplars that members of the specialty may have used over a specified time period, even though they may no longer be referred to.

The reason for this emphasis on the exemplar set rather than on individual exemplars is that both methodologically and theoretically, it is more satisfactory to consider groups of exemplars, rather than single exemplars. Thus, it has been suggested that the elements of a specialist matrix hang together to form a coherent framework, and of course, the exemplar set will constitute a part of that specialist matrix. But perhaps more importantly, it is impossible to tell, from examination of a single exemplar, what is the relevant aspect of that exemplar for current work, while if a number of relevant exemplars are studied, it is normally possible to see which aspects of the exemplars have been or are being developed. Thus, it is important to include that set of exemplars being used by members of a group, and it is particularly important to examine the exemplar set over time, as this most clearly indicates which aspects of the exemplars were developed, as well as indicating in which aspects they changed. In this sort of way, an understanding of the area of central concern of the specialty can be developed.

11.32 The specificity of the Specialist Matrix

Kuhn makes it clear in his postscript to The Structure of Scientific Revolutions that exemplars and other aspects of the matrix vary in power, specificity, and generality. Thus, he writes of revolutions:

... a few readers of this book have concluded that my concern is primarily or exclusively with major revolutions such as those associated with Copernicus, Newton, Darwin, or Einstein. A clearer delineation of community structure should, however, help to enforce the rather different impression I have tried to create. A revolution is for me a special sort of change involving a special certain sort of reconstruction of group commitments. But it need not be a large change, nor need it seem revolutionary to those outside a single community, consisting perhaps of fewer than twenty-five people.

(Kuhn :1970a:180)

Clearly the specialist matrix does not have to be very broad in order to lead to what Kuhn considers to be a paradigm based science. Yet this raises the further question -- how specific does a specialist matrix have to be before the research based on it can properly be seen as paradigm based?

If one considers the range of possible specificity for the various elements of the specialist matrix it becomes clear that much variation is on the cards. Thus, exemplars can be highly specific in all relevant technical and theoretical respects. They may be applied to situations in which no major extension is required, and if this situation were to continue for a time, they might come to constitute little more than a specific set of rules. X-ray crystallography, in many ways a very exact and specific set of procedures, tends towards this end of the spectrum. At the other end, as Mullins has shown, there was the early work of the phage group who in large measure possessed only certain general orientations about subject matter and large scale approach. Thus in this case the elements of the specialist matrix were so ill specified that they hardly constituted an adequate guide for scientific action.

11.33 Technique, Theory and Problem Based Specialties

Assuming then, that it is possible to locate communities of scientists in ways other than through the identification of

exemplary applications, there exists the empirical possibility that the investigator will discover actors who in their professional situation are scientists, who are in communication with one another about aspects of work, and thus on social grounds would be considered members of the same specialty, and yet these actors might not share strong exemplary guides to action, and other well specified aspects of the specialist matrix. This conclusion, which is of course, of particular interest in relation to the question of specialty formation, leads me to define and use the following terms:

1. A technique (or methods) based specialty is one in which the actors base their work on a set of exemplars that have to do primarily with the exploitation and development of the power and potentialities of a technique or set of techniques. Here the specialist matrix is reasonably well specified.

2. A theory based specialty is one in which the actors base their work on a set of exemplars that have to do primarily with the exploitation and development of the power and potentialities of a theory or a set of theories. This, like the technique based specialty, is one in which the exemplar set and the other components of the disciplinary matrix are reasonably well specified.

3. A problem based specialty is one in which the scientists have no well defined and precise exemplars over which there is agreement; none the less the members of the specialty work within a similar area, or they are concerned with what they define to be the same or similar problems. The problem based specialty is thus one in which the network attributes of the specialty are preserved, (except in so far as they relate to sanctioning action in relation to deviance from exemplars), but there is an absence of a well

specified shared achievement.

It should be clear that the above distinction is not a hard and fast one. It is heuristic, and in this instance primarily concerned with elucidating and further specifying the problem about the direction of scientific growth.¹

11.34 The Growth of Specialties

The distinction between specialties with well defined specialist matrices (theory and methods based specialties) on the one hand, and those with poorly specified specialist matrices on the other (problem based specialties), means that several paths for the development of new specialties can now be envisaged. It becomes an empirical matter as to whether a group of workers comes together and then generates a well specified exemplar set, or whether the process takes place in reverse order, starting with the achievement of an intellectual success -- or whether, indeed, the two processes take place simultaneously. This is a question that still has to be explored in practice, although Mullins' work on the phage group, which is discussed briefly below, suggests that in this case the social organisation may, to some extent, have preceded important subsequent cultural developments in the field.

1. The distinction, although drawn independently, is similar in some respects to that made by Pantin (:1968) between the "restricted" and "unrestricted" sciences. Thus, he writes:

The ... (biologies) are unrestricted sciences and their investigator must be prepared to follow their problems into any other science whatsoever. The physical sciences as they are understood, are restricted in the field of phenomena to which they are devoted. They do not require the investigator to traverse all other sciences.

(Pantin :1968:24)

11.35 Illustration of Notions of Technique Theory and Problem Based Specialties

In the following sections some implications of the notions of technique, theory, and problem based specialties will be worked out. This section will briefly illustrate the way in which these terms may be used.

1. Technique Based Specialty. British X-ray crystallography constitutes an example of a technique based specialty. This is because the actors "base their work on a set of exemplars that have to do primarily with the exploitation and development of the power and potentialities of a technique." Furthermore, the specialist matrix is well specified.

The empirical chapters of this work have traced the development of British X-ray crystallography from 1912 onwards, at first only in summary, and then in relation to work on proteins, in some detail. This work involved:

a. the establishment of a set of exemplars that concerned a particular technique, how to use it, and what to do with it. This was in the work of the Braggs, Mosely, Darwin, and to a lesser extent in the work of Laue, Ewald, and other German workers.

b. the development of X-ray crystallographic techniques in their application to ever larger crystal structures. Thus, the important contributions by W.L.Bragg, James, Bradley, Bernal, Lonsdale, Robertson, Crowfoot, Perutz, Kendrew, Crick, Astbury, and Phillips, among many others, were either mentioned or illustrated.

c. the specialist matrix was well specified, and although concerning other aspects of work (such as subject matters) was

primarily directed to the use of methods.

d. these workers were, on the whole, sufficiently well in touch with each other's work to be able to judge its competence.

e. there was a high degree of interaction between them. This can be seen through the master-pupil relationships, colleague groups, co-authoring, and mutual citation. Much of this data has not been presented in a systematic manner, and it is just possible that they interacted with non-crystallographers more than they interacted with each other. (Even in this case, British X-ray crystallography can still be seen as a technique based specialty in the cultural sense of the definition, on the basis of categories a - d.)

This data is more extensively discussed later in this chapter.

2. Theory Based Specialty. It is further suggested that German workers in X-ray crystallography were members of a theory based specialty. These workers were, on the whole, more interested in physical theory than in structure determination. Their work, then, involved:

a. the use of a set of exemplars, which although substantially overlapping with that of the British crystallographers, was none the less ultimately orientated to the development of theory:

For several years (1921 - 1924) the interest in structure determinations prevailed, but then the key role of X-rays and gamma rays for basic problems concerning the structure of radiation and matter (Compton effect, Geiger counter, light quantum hypothesis, dispersion theory) focussed attention on general questions of the physics of X-rays and electrons.

(Mark :1962:605)

b. the emphasis tended to be on basic elegance, rather than on the best ways of determining the structures of crystals:

... Paul Ewald used to put (the British lead in structure determination) down to what he called, not in any disparaging way, the peasant minded approach of the British! They thought

of things in simple ways, whereas the Germans always wanted an elegant finished theoretical analysis of everything that they did. (Lonsdale :1970:6)

It should be noted, of course, that the workers from these two different traditions were by no means using mutually exclusive sets of exemplars in their work. In the early years, at least, there was a high degree of overlap, and work by the Braggs, by Laue, and others, achieved exemplary status in both traditions. But this in itself, of course, re-emphasises the importance of considering not isolated exemplars, but rather exemplar sets, since it is clear that the same journal article may be developed in different respects by different actors.

3. Problem Based Specialty. It is suggested that at an early stage in its development, the phage group constituted a specialty which resembled the above definition of a problem based specialty. Thus, as the earlier discussion of Mullins' work has shown, the members of this group were all working in a similar area, and were concerned with what they defined to be the same or similar problems. Despite this they did not share very clear guides to scientific action. Thus, it will be recalled that Mullins wrote:

The group's paradigm, formally stated, became: Studying phages to solve the problem of genetic information transmission with as precise methods as could be developed. This paradigm, like most real paradigms, was not initially very precise, but it would become more precise as time and work passed. A very important event for this paradigm occurred when norms were established to govern the kinds of research done and the manner in which it was done and presented. (Mullins :1971:9)

Although Mullins has argued that the network aspects of the group were not well developed (in his terms, they were at "paradigm group" or "social network" stages), there was nevertheless some communication between the workers who were later to become the centre of the specialty.

Thus, although the phage group constitutes what is, perhaps, a rather marginal example of a problem based specialty, it suggests that other, similar groups, with better developed social network structures may exist at certain points in science.

11.36 Paradigms and Exemplars

The term exemplar, in particular, and Kuhn's later, rather than his earlier vocabulary, in general, have been employed in the above. This is because of certain drawbacks in the accepted use of the term, paradigm.

11.361 Excessive Legislation

Kuhn, in his original account, tends to legislate on matters that might, more satisfactorily, be left open to empirical observation. In the above account the emphasis has been on flexibility -- specialties have been defined both in terms of network and cultural attributes, specialist matrices of various degrees of specificity have been envisaged, various paths for the development of specialties have been mentioned, and in general, a less rigid account of possible changes in meaning and practice in the process of normal science has been offered. While none of this strays from a broad Kuhnian framework, it has been designed to cast light on the internal mechanisms that affect the direction of scientific growth.

1. Global paradigmatic changes followed by periods of relative quietude may or may not constitute an adequate description in the case of the exact sciences -- those that Kuhn has most depended on such as astronomy and physics. Whether such a description is applicable in areas of "softer" science such as many areas of biology, is an open question. In using Kuhn's later vocabulary,

the author does not propose to commit himself to a stepwise scheme of scientific change which dominates Kuhn's original account. His purpose is to account for possible changes in normal science situations, and he feels that Kuhn has to some extent underestimated the degree of change possible without revolutionary situations. The succession of exemplars in protein crystallography, for example, which will be mentioned a little later on, constitutes a set of important changes in a specialty that is, perhaps, nearer to Kuhn's "hard" science examples than most.

2. Although this is not, perhaps, Kuhn's fault, the assumption of a high degree of cognitive consensus within the paradigm and specialty again constitutes an example of unwarranted legislation. There has been no satisfactory discussion of the relationship between authority and patterns of innovation, and this will be necessary before a full understanding of the development and acceptance of exemplars will be achieved. Thus, it would be necessary to investigate the manner in which potential exemplars are received by members of the specialty. To what extent are exemplars imposed on unwilling subordinates, and to what extent is the consensus that is seen in specialties a real one? Work on this subject has been carried out by Mullins and French, but no systematic approach has yet been adopted by any worker.

11.362 The Direction of Scientific Growth

A further drawback concerning the term paradigm, and the notion of the articulation of paradigms, is that although Kuhn explains how the activity of articulation might operate, he does not offer a general approach to the problem of the direction of articulation. This question is, in large measure, a sociological one, and a

solution to the question will refer to group standards, rewards, and scientific identities. It is easier to approach this problem via a discussion of exemplars, exemplar sets, and other aspects of the specialist matrix, than it is through discussion of paradigms.

11.363 Social and Psychological Definition of Paradigm

There is a final, and potentially fatal objection to Kuhn's definition of paradigm, that further recommends the use of exemplar, and the approach discussed above. In the Structure of Scientific Revolutions paradigm is defined both psychologically (and by implication philosophically) and sociologically. Kuhn's approach depends to a fair extent on gestalt psychology, and he tends to talk about paradigm change in terms of jumping through a conceptual hoop. Thus, he writes:

Examining the record of past research from the vantage of contemporary historiography, the historian of science may be tempted to exclaim that when paradigms change, the world itself changes with them. Led by a new paradigm, scientists adopt new instruments and look in new places. Even more important, during revolutions scientists see new and different things when looking with familiar instruments in places they have looked before. It is rather as if the professional community had been suddenly transported to another planet where familiar objects are seen in a different light and are joined ... by unfamiliar ones as well. ... paradigm changes ... cause scientists to see the world of their research-engagement differently. In so far as their only recourse to that world is through what they see and do, we may want to say that after a revolution scientists are responding to a different world.

It is as elementary prototypes for these transformations of the scientist's world that the familiar demonstrations of a switch in visual gestalt prove so suggestive. What were ducks in the scientist's world before the revolution are rabbits afterwards. (Kuhn :1970a:111)

He continues:

The world that the student ... enters is not, however, fixed for once and for all by the nature of the environment, on the one hand, and of science, on the other. Rather, it is determined jointly by the environment and the particular normal-scientific tradition that the scientist has been trained to pursue. Therefore, at times of revolution, when normal-scientific

tradition changes, the scientist's perception of his environment must be re-educated -- in some familiar situations he must learn to see a new gestalt. After he has done so the world of his research will seem, here and there, incommensurable with the one that he had inhabited before. That is another reason why schools -- guided by different paradigms are always slightly at cross-purposes. (Kuhn :1970a:112)

In this understanding of paradigm, then, there is a notion about shared gestalt switch (even if this constitutes an analogy rather than an exact representation of what goes on at a scientific revolution). There is meaning shift at the point of paradigm change, and in this respect, in this view paradigms have both psychological and philosophical implications.

However, in addition to this, paradigms also have social implications (which are, of course, obvious in the above), and on occasion the social meaning of the term may conflict with the philosophical meaning. Consider the social meaning of the term. Kuhn writes:

In this essay, 'normal science' means research firmly based upon one or more past scientific achievements, achievements that some particular scientific community acknowledges for a time as supplying the foundation for its further practice. Today such achievements are recounted, though seldom in their original form, by science textbooks, elementary and advanced. These textbooks expound the body of accepted theory, illustrate many or all of its successful applications, and compare these applications with exemplary observations and experiments. Before such books became popular early in the nineteenth century ... many of the famous classics of science fulfilled a similar function. Aristotle's Physica, Ptolemy's Almagest, Newton's Principia and Opticks, Franklin's Electricity, Lavoisier's Chemistry, and Lyell's Geology -- these and many other works served for a time implicitly to define the legitimate problems and methods of a research field for succeeding generations of practitioners. They are able to do so because they shared two essential characteristics. Their achievement was sufficiently unprecedented to attract an enduring group of adherents away from competing modes of scientific activity. Simultaneously, it was sufficiently open-ended to leave all sorts of problems for the redefined group of practitioners to resolve. Achievements that share these two characteristics I shall henceforth refer to as 'paradigms', a term that relates closely to 'normal science'. (Kuhn :1970a:10)

Here, then, a paradigm is referred more explicitly to the social structure, and much less explicitly to psychological and philosophical points of reference (although these are clearly implied). Yet, as was suggested above, the social meaning may conflict with the psychological or philosophical meaning. An achievement may be received by a group who work on its articulation, when that achievement is, itself, part of the normal science process of articulation in another (and possibly overlapping) group. This is not merely a definitional point, because it can lead to difficulty in deciding whether a particular achievement really constitutes a paradigm, or not.

For this reason, in the earlier discussion of specialist matrices and specialties, it was made clear that the degree to which a specialist matrix or an exemplar set varied over time or space was a matter that was open to empirical study.

A problem of the nature outlined above arises in the early history of X-ray crystallography, although the data for this early period have not been presented in detail in the empirical chapters. It may be briefly summarised as follows.

X-ray crystallography constitutes an area of normal science, with its own textbooks, received achievements, and classic papers. Thus in the very early days, the papers by the Braggs, by Laue, Ewald, Mosely, Darwin and Debye amongst others achieved exemplary status, and it seems that the Braggs' textbook X-rays and Crystal Structure, which went through at least four editions between 1915 and 1924, achieved similar status, at least in the British community of X-ray crystallographers. This early work attracted a group away from competing areas of scientific activity, if not competing modes

of scientific activity. Obviously this achievement was sufficiently open ended to leave much room for problem solving activity. Therefore, in terms of the social definition of the paradigm outlined above, this work was paradigmatic.

On the other hand, the development of X-ray crystallography in this early work did not involve any major conceptual or psychological changes. It was, in all important respects, a development of normal science -- the opening up of an area of ignorance by means that were already well known at the time of the discovery. Thus, although there was controversy about the nature of X-rays¹, the notion that they were a wave phenomenon constituted no radical departure for any of the workers concerned, and the nature of diffraction had been fully worked out for light and even for X-rays, in the case of a two dimensional grating. Since the notion of the crystal lattice was also current, although in the rather different community of crystallographers, all that was required was the unification of various already existing and well articulated ideas -- the behaviour of wave radiation in a lattice, the notion that X-rays are waves, and the notion of the crystal lattice as a diffraction grating -- in order to start a new research tradition.

I do not wish to underestimate the genius or innovatory power of some of the early workers in making such an assertion. What I wish to do rather, is to suggest that for most workers at least,

1. There was an outstanding controversy between Barkla and W.H.Bragg as to whether X-rays were a wave or a corpuscular phenomenon. The new experiments on X-ray diffraction demonstrated to the satisfaction of all concerned, that the former was the case.

nothing comparable to a gestalt switch occurred. Certainly nothing akin to a scientific revolution took place. Various pre-existing elements were combined in a manner obviously and immediately acceptable to all the physicists concerned, to make a new technique which opened up a new area of inquiry. Some physicists chose to work in the new area, and some chose to work in other areas, but the choice before them was not one to be made on major conceptual grounds. The various areas were not only commensurable -- they were also highly compatible.

The early work has exemplary status, therefore, but it is not revolutionary, and does not entail paradigm shift. Yet is it not, in terms of the second definition, surely a paradigm? In view of this difficulty I have followed Kuhn in abandoning the use of the term paradigm. In using the specialist matrix and its components, the definition is in the first instance sociological -- it relates to shared achievements. How different these achievements are from those of other groups, to what extent are they shared by other workers -- these are matters for empirical investigation. The investigator must be constantly aware of the possibility of meaning shift, but this is not legislated into each change in the exemplar set. This more flexible vocabulary is more suited to a detailed account of scientific change than the ambiguous, large scale, paradigm.

11.4 Further Development of Theoretical Approach

The notions of technique, theory, and problem based specialties have been developed above, and illustrated, in an approach to the central interest of this chapter -- the structure and reasons for

the growth of a normal science tradition in one particular direction rather than another.

11.41 Permissible and Impermissible Types of Work

In any specialty with a well defined specialist matrix there are certain classes of work which actors will consider relevant and acceptable, and others which they will consider irrelevant or unacceptable. This is a distinction of some importance, and relates to the exemplar set, and the other components of the specialist matrix. Those types of work that are seen as being potentially articulable -- those areas where the specialist matrix is seen as having some relevance -- constitute acceptable areas of work. This distinction will be known henceforth as the distinction between permissible and impermissible types of work.

The actor will know, or at least have a good idea, that certain types of work are impermissible, and he will know or suspect that if he engages upon them in his professional capacity he will be negatively sanctioned by other actors in the specialty. It is not suggested that permissible and impermissible areas of work remain the same over time, and neither is it suggested that there is a clear borderline between the two. In this definition the permissible types of work will be seen to include all possible borderline cases, so it is only clearly impermissible classes of work that are to be included in the impermissible category. Considerable misuse of theories or methods, or work in an inappropriate area, would constitute impermissible types of work, and it is appropriate to talk in terms of deviance in this case. Velikovski was a deviant, both in terms of the methods and the theoretical schemes that he introduced into astronomy. Wrinch was deviant in her unacceptable

use of Patterson diagrams in crystallography. Both these actors were the objects of negative sanctioning, for the clear reason that they cut across the scientific expectations of their peers in obvious ways.

This distinction is not, in itself, all that novel. It is implicit in the work of both Kuhn and Hagstrom, and it obviously bears a very close relationship to the specialist matrix, and the exemplar set. The novelty here constitutes only in coining the terms, and this is done for heuristic purposes.

Since the technique based specialty is partly defined in relation to an exemplar set which indicates that the central concern of the practitioners is the development of a particular technique or set of techniques, this means that there are standards which indicate that certain methods are appropriate, and that certain ways of applying, making use of, and developing these methods are appropriate. Thus, it is clear that what would constitute permissible and impermissible types of work in a technique based specialty would, in the first instance, relate to the kinds of methods used, and the manner of their employment. If the methods that are perceived as being appropriate are used in the appropriate manner, then this would constitute a permissible type of work. In a technique based specialty, the distinction between permissible and impermissible made in this way is likely to be fairly clear, as a large part of the class of exemplars in the exemplar set at any one time will relate to methods, and to the use of methods.¹

1. This argument is now followed only for the case of the technique based specialty. However, the analogous case is true for the theory based specialty, where theoretical considerations would be most clearly spelled out in the specialist matrix, and thus there would normally be a clear distinction between permissible and impermissible use of theory.

Further, and this is important, the scientific identity of the actor bears a close relationship to the nature of the exemplar set. In a specialty of the technique based type, identity will typically revolve around the use of appropriate techniques. This can frequently be seen to be true in terms of ascribed status -- workers describe themselves or others as X-ray crystallographers, experts on NMR, radioastronomers, electron microscopists, and so on. This sort of scientific identity is built up in the course of extensive socialisation during which the student is familiarised with that set of exemplars surrounding the use and exploitation of a particular technique or set of techniques. At the end of their training, the students are typically welcomed to the specialty where they carry out further work on the development of techniques, while at the same time reinforcing their status and identity connection with the technique.

Of course, as was mentioned in the first section, scientific identity does not bear a simple relationship to the types of theories and methods used. Fisher has argued convincingly that the classification of mathematics in certain areas into different groups is primarily a social rather than an intellectual phenomenon. It is only suggested that as a first approximation, identity bears a strong relationship to the exemplar set.

Thus, most of the workers discussed in the empirical sections regarded themselves as X-ray crystallographers, although interestingly enough, few of them trained as crystallographers extensively in their first degrees. Those that did not regard themselves as crystallographers -- Lonsdale and Astbury, for example -- constitute

the exception rather than the rule.

11.42 Preferred and Non Preferred Types of Work

It is argued above that in the case of the technique based specialty, the line between permissible and impermissible types of method is fairly clear, since the exemplar set directly specifies the nature of the methods. However, the distinction between permissible and impermissible subject matters is typically much less clear, since it is neither so well specified, nor of primary importance to the identity of the practitioner. Strong elements of identity are not involved in the first instance, and the exemplary control of subject matters is normally an indirect process, working through the methodological standards.

This may be clearer if it is spelled out in practice. In the case of X-ray crystallography, there is a set of exemplary techniques, and appropriate uses. In most cases the identity of the crystallographer revolved around these techniques and their uses. The type of subject matter was not of primary importance. Of course, X-ray crystallography, like most sophisticated techniques, is sensitive to only a very limited class of phenomena -- diffracted X-ray beams -- so this inevitably limits the type of substance that can be used for study. The material must be crystalline or semi crystalline (although this definition is in many respects a social one). Inside the large class of substances that can be approached by the method, however, anything is fair game for the crystallographer. He receives no direct guidance about the types of crystals that will be appropriate for study. Such guidance as is forthcoming from the exemplar set comes indirectly, and is of the form -- is this a crystal that can be approached given the present state of

development of the technique.

Yet, of course, the question as to what constitute preferred types of work is of great importance in a discussion of the direction of scientific growth. Within the area of permissible work, then, there are some areas which the community of specialists finds it important, desirable, and pressing to study, and there are other areas which, while permissible, are not seen as being important and desirable. There are two factors that affect the degree of preference attached to any area:

1. The perceived difficulty of the problem area.
2. The perceived importance of the problem area, which bears a strong relationship to the expected reward to be gained if the problem is solved.

In general one would expect to find that there was concentration on problems that were perceived to be both not too difficult, and yet also important. Each of these aspects will be briefly considered.

In large measure, the perceived difficulty of a problem depends on the relationship between the existing problem solutions and exemplars, and the problem that is to be tackled. Thus, if a close relationship between an existing problem solution and the problem to be approached is seen, then the problem will not be considered difficult. If, on the other hand, it is not clear how any existing problem solution can be extended to apply to the new case, then the problem will be perceived as difficult. This will especially be the case if it is believed that there is some systematic and fundamental difficulty in the way of a successful problem solution, and if, for example, the same kind of difficulty has arisen on

previous occasions.¹

The question about the nature of those problems that are perceived to be important in the end reduces to a question about the types of demands that are made on the actor. Many demands are made on the actor by others in his own specialty, and these, as has been noted, relate primarily to the development of the technique. Thus, subject matters will be chosen because they contribute to the development of the technique. However, not all the demands come from members of the specialty. Particularly in the case of the technique based specialty, where aspects of the work are of intrinsic interest to members of other specialties, there will be demands for work on specific subject matters which are of particular interest to members of the specialty concerned. Clearly the practitioner of the technique based specialty will be positively sanctioned if he provides a solution that is thus of interest, and he will gain prestige.

It is, of course, a real possibility that the demands of outsiders will conflict with demands of other members of the specialty, and what constitutes the preferred areas of work for any actor will depend on who is in the position to make the strongest demands, and exert the strongest sanctions. In general, one would expect the specialist colleague group to be in the strongest position in this respect, but of course, this is not always the case. The preferred areas of work will thus depend on both the

1. This is one area in which Mulkay's work on attitudes to risk taking may be applicable. If he is correct, then one would expect middle status workers who have much to lose and little to gain, to work on problem areas perceived to be easy. High, and very low status workers might work on difficult problems. However, it will be necessary to gain a highly sophisticated picture of the actor's view of difficulty.

perceived difficulty of the problem (something that is likely to depend on the specialist colleague group only) and on the degree of demand and interest attached to a solution (something that will depend on workers both within and outwith the specialty).

This approach to the causes of the direction of scientific growth will be illustrated in a further section in relation to the data on protein X-ray crystallography assembled in Chapters Two to Nine.

11.43 Specialist Utopias

In view of the differences in socialisation, subtle differences in the exemplar sets, and differences in demands made on actors, one would expect that despite general concentration on certain areas, there would none the less be quite a wide range of problem solving being undertaken ¹. This is also affected by what I shall call a "specialist utopia".

Mannheim, in his discussion of utopias, baldly writes:

A state of mind is utopian when it is incongruous with the state of reality within which it occurs. (Mannheim :1960:173)

A little later he writes:

Only those orientations transcending reality will be referred to by us as utopian which, when they pass over into conduct, tend to shatter partially or wholly, the order of things prevailing at the time. (Mannheim :1960 :176)

The term has been used, in the context of science, by Hagstrom:

Every established discipline possesses an ideology, a more or less explicit justification of its privileges and the claims it makes upon the scientific world and the larger society.

1. This would also result from factors such as those discussed by Mulkay and Turner (:1971), who consider the relationship between innovation and competition.

These ideologies are partly alleged facts about the contribution, of the discipline, and partly evaluations about what is or should be considered 'interesting' and 'intrinsically important'.
(Hagstrom :1965:211)

Of utopias, he writes:

Corresponding to the ideologies of established disciplines are the utopias of newly emerging disciplines, justifications of proposed changes in the structure of science whereby the new discipline will gain a more secure position. (Hagstrom :1965:212)

The way in which the term is used here is somewhat different from that employed by both Mannheim and Hagstrom, although it will be clear that there are, in fact, strong similarities. I will define a "specialist utopia" as an image of possible future development of the intellectual and social structure of the specialty which has not been achieved, but which is none the less perceived by the actor. This definition covers both cultural and social aspects of specialty development, but the relevant aspect at this point concerns cultural change alone.

I wish to describe this "image" of future development as something more than a simple long term goal, for several reasons. The first, and most obvious, is that it is less specific than a goal. The achievement of any particular piece of work would not constitute the achievement of a scientific utopia, which by its definition, cannot be achieved. Secondly, although it is perhaps a little strong to argue that utopia in the sense defined above, is "incongruous" with the state of reality within which it occurs¹, none the less, the sense in which it is defined here fits with another aspect of Mannheim's definition, where the latter notes that

1. There are, after all, elements in the situation of the actor that can (or so he hopes) be made congruent with the utopia.

utopias "orients conduct towards elements which the situation, in so far as it is realised at the time, does not contain". The "order of things" is partially shattered, in the sense that old exemplars, and other aspects of the specialist matrix, are discarded (once having been built upon) in the development of work in the direction of a utopia. The usage defined above conflicts with Hagstrom's use of the term, in that it is clear that utopias can be developed and held by practitioners in already established disciplines or specialties, and are not restricted to those specialties that are trying to gain a more secure foothold in the structure of science.

So, utopia in this sense is seen as a general expression of a desired state of affairs, although it is more general than a goal. The utopia does not, as such, help in the solution of any particular problem, and it cannot, by definition, be achieved. It is, in the cultural sense, a declaration about the solution of a class of problems, the development of powerful techniques, and all embracing theories that solve existing problems.

In the case of X-ray crystallography, the specialist utopia typically consisted of the desire to greatly advance techniques and solve crystal structures that were impossibly difficult at the time -- proteins and viruses for example.¹

The specialist utopia bears a relationship with both the specialist matrix and the exemplar set on the one hand, and with the scientific identity and status of the actor on the other. The

1. The solution of one protein, however, would not have resulted in the achievement of the utopia. At this point the utopia might have changed its expression, and have been represented as a desire to solve the structure of water and gases, for example.

nature of the specialist utopia clearly depends on the scientific identity of the actor -- only a crystallographer will, after all, dream about the solving of structures of very complicated crystals. It also bears an indirect relationship to the exemplar set, for although no presently conceivable extension of the exemplar set would result in the achievement of the specialist utopia, none the less many extensions of the exemplar set will be seen as a move in the direction of the realisation of the utopia. It thus depends on the exemplar set, but at the same time helps to emphasise its dominant line of development, and gives direction to future work.

The specialist utopia may thus, under some conditions, lead workers to approach problems that are difficult, but which are seen as being important steps towards its realisation. There is some evidence to suggest that it worked in this way in the cases of W.L. Bragg and Bernal.

11.5 Norms and Exemplars

In the above the term "exemplar" has been extensively used, but there has been no reference to "norm". Obviously the two are, in many respects, very similar, fulfilling the same function -- indicating actions that are, or are not acceptable, in any given social group. Why, then, has the term exemplar been so extensively used, and the term norm not employed? In this section, certain implications of the term "exemplar" are examined, and compared with habitual modes of using the term norm, and it will be suggested that, not only is the term exemplar more suitable in the context of a discussion of science, but it may turn out to be useful in other areas of sociological inquiry.

11.51 Conventional Uses of the Term "Norm"

In a section of this length it is impossible to offer a satisfactory discussion of "norm". Rather, three general approaches will be typified in the work of three authors -- Merton, who views norms as precepts, Sherif, who adheres to a fundamentally behaviourist view, and Gross, who in using the term expectation, emphasises that normative consensus is problematical.

11.511 Merton

Norms are seen in the context of a functionalist framework. But more than this, they are typically reported by Merton in the form of explicit statements from the actor's point of view. Thus, Merton writes:

The institutional goal of science is the extension of certified knowledge. The technical methods employed to this end provide the relevant definition of knowledge: empirically confirmed and logically consistent predictions. The institutional imperatives (mores) derive from the goal and the methods. The entire structure of technical and moral norms implements the final objective. The technical norm of empirical evidence, adequate, valid, and reliable, is a prerequisite for sustained true prediction; the technical norm of logical consistency, a prerequisite for systematic and valid prediction. The mores of science possess a methodologic rationale but they are binding, not only because they are procedurally efficient, but because they are believed right and good. They are moral as well as technical prescriptions. (Merton :1957:552)

Merton's attitude to norms comes out even more explicitly in his contribution to The Student Physician:

The profession of medicine, like other occupations, has its own normative subculture, a body of shared and transmitted ideas, values and standards toward which members of the profession are expected to orient their behaviour. The norms and standards define technically and morally allowable patterns of behaviour, indicating what is prescribed, preferred, permitted, or proscribed. The subculture, then, refers to more than habitual behaviour; its norms codify the values of the profession.

(Merton, Reader and Kendall :1957:72)

In Merton's view, the norms of the medical profession are patterned

in two major respects:

First, for each norm there tends to be at least one coordinate norm, which is, if not inconsistent with the other, at least sufficiently different as to make it difficult for the student and the physician to live up to them both. ... From this perspective, medical education can be conceived as facing the task of enabling students to learn how to blend incompatible or potentially incompatible norms into a functionally consistent whole. (Merton, Reader and Kendall :1957:72)

Secondly, "the values and norms are defined by the profession in terms of how they are to be put into effect" and they are seen as requirements of the physician's role.

The first of these characteristics, the matching of potentially incompatible norms in pairs, is seen by Merton as a typical characteristic of social institutions. Thus, he produces a similar set of norms in science (Merton :1965) noting that they are "garnered from the literature of science". In so far as they are contradictory, the norms cannot be fully translated into action. On the other hand, norms of the sort discussed above are clearly taken from the actor's point of view.

An implication of the Mertonian view of norms is that it is clear and unambiguous as to what sorts of actions would constitute deviance. In as much as the conflicting norms are not blended into a consistent whole, the actor is of necessity condemned to acts of deviance.

To summarise, Merton's norms are moral prescriptions, expressed verbally, and clearly indicating what constitutes deviance.

11.512 Sherif

Sherif uses the term norm in a behavioural manner, although this is often paralleled by the actors attitudes and perceptions:

We shall consider customs, traditions, standards, rules, values, fashions, and all other criteria of conduct which are standardized

as a consequence of the contact of individuals, as specific cases of "social norms". (Sherif :1966:3)

Mulkay, who makes use of Sherif's account of norms in his discussion of Kuhn's paradigms, also quotes the following passage:

... norms serve as focal points in the experience of the individual, and subsequently as guides for his actions. This need not always be a conscious function; many times it is effective without our awareness of it. We see the evidence of its effectiveness by its results, that is, in the behaviour of the individual. The daily routine of everyday life is regulated to a large extent by the social norms in each society. As long as life with its many aspects is well settled and runs more or less smoothly from day to day, very few doubt the validity of existing norms; very few challenge their authority. And the few who challenge them are considered to be doubting Thomases, eccentrics, trouble makers, or lunatics, and they are reacted against with varying degrees of scorn or violence.
(Sherif :1966:85)

Breaking the norms, under normal circumstances, therefore attracts negative sanctioning. Indeed, one of the main ways of inferring the nature and existence of the norms must be in terms of the negative sanctioning of deviants . Sherif clearly sees many norms as organising experience -- that is to say that they may have cognitive status. Thus, he writes:

These interiorized social norms enter as frames of reference among other factors in situations to which they are related, and thus dominate or modify the person's experience and subsequent behaviour in concrete situations. ...
... In one society the norms and taboos in the cultural background may emphasize similarities among certain individuals who stand in a certain relationship to one another, or may deny such similarities, and as a consequence the individuals are not thought of as standing in this relation to one another. Such established norms or standards are not rigid, unchangeable entities ... (Sherif :1966:44)

In brief, then, for Sherif norms may have cognitive status, the process of internalising them is, at least in part, unconscious, and there is a well defined notion of deviance.

11.513 Gross, Mason and McEachern

These writers do not use the term norm, but employ the term

expectation, thus emphasising the questionability of normative consensus. They write:

An expectation will be defined as an evaluative standard applied to an incumbent of a position. (Gross, Mason and McEachern :1958:58)

Thus, evaluations are defined from the actor's point of view.

Essentially, the authors suggest that there are two problems that cannot be ignored in any discussion of role. First, it is necessary to specify the population of role definers, for the expectations that attach to a focal position vary according to the status of the definer. Secondly, it is necessary to specify the level of generality. They note:

It is possible to study expectations at many levels of generality, general functions and microscopic acts perhaps illustrating two extremes. (Gross, Mason and McEachern :1958:71)

The population of role definers is very important. There may, obviously, be different expectations on the part of different definers. Furthermore:

Presumably each role definer would have an expectation with regard to each of the possible alternatives. We may raise the following questions for a specified set of role definers: Is there agreement, for example, as to which of the alternatives are acceptable? Is there an agreed upon order of preference among the alternatives? The alternatives for the situation can be of two types: they may fall along a continuum, or they may be qualitatively different.

(Gross, Mason and McEachern :1958:73)

To summarise, the process of internalising expectations is in large measure dependent on their verbal expression. Sanctioning action for deviance may vary.

11.52 Use of the Term "Exemplar"

One important aspect of the exemplar has already been stressed -- namely the element of direct modelling by following the example of a teacher. It was suggested that many of the operations involved

in driving a car were not of the sort that could be fully verbalised -- even though there might be textbooks about driving cars, in which many of the more important necessities were written down.

A second important aspect of exemplar arises in Kuhn's argument against the falsification criterion of demaraction developed by Popper. Kuhn notes that Popper's recently elaborated measure of verisimilitude:

requires that we first produce the class of all logical consequences of the theory and then choose from among these, with the aid of background knowledge, the classes of all true and of all false consequences. ... None of these tasks can, however, be accomplished unless the theory is fully articulated logically and unless the terms through which it attaches to nature are sufficiently defined to determine their applicability in each possible case. In practice, however, no scientific theory satisfies these rigorous demands, ... (Kuhn :1970b:16)

He goes on to discuss the knowledge that an actor might have about "swans" and asks how much it is possible to know about swans without introducing explicit generalisations. He suggests, after Wittgenstein, that there is no good reason to make such generalisations as they serve no cognitive function. He concludes with a general statement which expresses the core of his argument as it applies to scientific knowledge:

I suggest that scientific knowledge, though logically more articulate and far more complex, is of this sort. The books and teachers from whom it is acquired present concrete examples together with a multitude of theoretical generalisations. Both are essential carriers of knowledge, and it is therefore Pickwickian to seek a methodological criterion that supposes the scientist can specify in advance whether each imaginable instance fits or would falsify his theory. The criteria at his disposal, explicit and implicit, are sufficient to answer that question only for the cases that clearly do fit or that are clearly irrelevant. These are the cases he expects, the ones for which his knowledge was designed. Confronted with the unexpected, he must always do more research in order further to articulate his theory in the area that has just become problematic. He may then reject it in favour of another and for good reason. But no exclusively logical criteria can

entirely dictate the conclusion he must draw.¹
(Kuhn :1970b:19)

This puts, very clearly, Kuhn's use of exemplar. Scientific problems are unexpected, and the possible puzzle solutions are unanticipated. There is an intermediate territory between that group of puzzle solutions that consider classes of phenomena where the family resemblances are clear, and that class of puzzle solutions that clearly attempt to assert family resemblances where none are perceived to exist. In the intermediate territory the puzzle solutions cannot be seen as being fully rule bound in the sense that it is a priori obvious that they are either acceptable or unacceptable. There is no basis upon which to make a priori judgements. It is necessary, as Kuhn suggests, to do further work. It is presumably necessary to consider the complex web of family resemblances, and the situation and problems of each actor. As Kuhn wrote in the above, "the criteria at his disposal, explicit and implicit, are sufficient to answer the question only for the cases that clearly do fit or are clearly irrelevant. These are the cases he expects,

1 Compare this with Wittgenstein's discussion of the use of the word "game", when he argues that the latter is normally used in a manner that is not closed by a boundary:

And this is how we do use the word "game". For how is the concept of a game bounded? What still counts as a game and what no longer does? Can you give the boundary? No. You can draw one; for none has so far been drawn. (But that never troubled you before when you used the word "game".)

"But then the use of the word is unregulated, the 'game' we play with it is unregulated." -- It is not everywhere circumscribed by rules; but no more are there any rules for how high one throws the ball in tennis, or how hard; yet tennis is a game for all that and has rules too. (Wittgenstein :1968:33)

Kuhn can be seen as having extended Wittgenstein's discussion to the case where a decision about a potential new member has to be made -- is the family resemblance sufficiently striking to allow the actor to include the potential new member in the family, or not?

the ones for which his knowledge was designed." (My italics).

To summarise the above, then, Kuhn's notion of the exemplar stresses the element of direct modelling (although there are other aspects of the specialist matrix where this is not the case), it emphasises that scientists can act without in all cases being able to talk about it, and it loosens up the notion of deviance, rendering it at least in part irrelevant for those cases for which the knowledge was not explicitly designed.

11.53 Comparison of Norm and Exemplar

Although norms are in some ways similar to exemplars, and this similarity varies according to the definition of norm adopted, the following section, which compares the usages of the two, suggests that there are some major differences that justify the use of exemplar rather than norm in the theoretical approach to scientific growth.

11.531 Specificity

The Mertonian norms are very general, although he sees them as being translated into specific guides to action. It has been argued earlier in this chapter that the norms do not guide action in a great many cases. However, even leaving empirical doubts aside, his norms could not be said to constitute a sufficient guide for action, for other reasons. Thus, to prescribe "scepticism" as a general norm does not lead to an easy translation in specific instances except, conceivably, in a positivist world view. Therefore, although Mertonian norms do not, perhaps, conflict with the notion of the specialist matrix, they could hardly be said to refer to the same class of actions. It is possible that some of Merton's norms have validity at a general level, but the discussion

here is concerned with much more detailed working of science.

Sherif's notion of norm would clearly include what Mulkay has called cognitive or technical norms -- detailed specifications of appropriate actions in scientific situations. In this sense, Sherif's norms are at the same level of specificity as Kuhnian exemplars.

The level of generality of the expectations discussed by Gross varies widely with the population of role definers, and the interests of the sociologist. At their most detailed they have relevance for detailed technical prescription.

It may, therefore, be argued on grounds of specificity, that Sherif's and Gross' use of the term norm or expectation is consistent with Kuhn's use of the term 'disciplinary matrix'. Merton's use of norm, however, is not.

11.532 Direct Modelling

A vital notion in exemplar is that of direct modelling -- the modelling of actions on previous actions. This is not something that is stressed in any of the accounts of norms given above, although it is consistent with the account offered by Sherif, who does not insist that norms have to be explicit. In as much as the accounts offered by Merton and Gross depend on explicitly stated evaluations, then they tend to diverge from Kuhn's account of exemplar.

11.533 Deviance

To Kuhn, the notion of deviance is obviously inapplicable in some cases of innovative action -- all those cases for which the knowledge was not specifically designed. Sherif, whose notion of

norm is essentially behaviourist, cannot easily locate the norms except by sanctioning actions, under normal circumstances. It is only when "social life becomes difficult" and norms tend to break down that important and unstructured innovation would seem to take place in his view. Mulkay may be right to equate this kind of innovation with that which occurs during scientific revolution, but this is not the situation in the case of innovation that takes place during normal science practice. It can be argued from a Kuhnian position that notions of conformity or deviance are in large measure inapplicable to normal science innovations, because there is not a complete set of prior rules (of whatever kind) that applies to the innovation. It follows that unless Sherif includes in his notion of norm, an area between acceptable and unacceptable action then his use of the norm is not tenable in this instance. He does not discuss this possibility, and although it seems contrary to the spirit of his behaviourist approach, it must none the less be allowed as possible from his point of view.

The case of Gross presents a different problem. His approach is more subtle, and allows for varying reactions depending on the position of the role definer. He also allows that the role definer may have a gradation of responses all the way from "highly acceptable" to "totally unacceptable". This is a sophisticated approach which is likely to be important in describing many situations. However, he does not succeed in evading the fundamental problem -- he too formulates the responses of the actor confronted with action in terms of an implicit list of possible alternatives, in much the same way that Popper demanded in his measure of verisimilitude. In doing so Gross falls into the same trap as

Popper. In the case of innovative action, such a list cannot and has not been drawn up. To use the term "expectation" about future innovation is, in a literal sense, nonsense.

11.534 Innovation

Possibly the most fundamental difficulty in using the term norm is in the context of innovative action. None of the uses of the term that has been discussed positively helps us to understand the nature of innovation in normal science. If the process of innovation can be seen in many respects as the demonstration of similarity relationships of various kinds, then the notion of specialist matrix and exemplar is helpful. With the manipulation of symbolic generalisations, the creation of new exemplars, we have the rudiments of an understanding of the process that does not inevitably lead to the notion that all innovation is deviant. This does not mean that there is room for complacency -- we have as yet no understanding of the reasons for the varying reception given to innovations. The achievement is a negative one -- we merely argue that the sociology of deviance is not relevant in many areas of normal science. It is perhaps the close connection between norms and ideas of deviance that constitutes the biggest obstacle to our use of the term.

11.54 Conclusion

The above, for convenience, is summarised in Figure 13. It is not meant to provide an exhaustive analysis of the term norm, or the difficulties of that term in discussions of innovation. It may be that the term can still be reclaimed and used in a manner that avoids the above difficulties. The above is rather designed to show why this author has avoided using norms in the theoretical

	SPECIFICITY	DIRECT MODELLING	DEVIANCE	INNOVATION
MERTON (NORM)	Not normally specific guides to action (unless seen from a positivist and empiricist view)	No. Usually reported verbally	Normally clear and unambiguous	Explained by applying norms to separate and unproblematical knowledge
SHERIF (NORM)	May be specified in detail	Yes, this is possible	Normally clear and unambiguous, except where norms are inadequately specified	Does not help in explaining innovation in 'normal science' situations.
GROSS (EXPEC-TATION)	Varies. May be very specific	Not normally relevant. Internalisation through verbalisation	Varies in different cases, but is related to previous expectations.	Not considered and seemingly not easily catered for.
KUHN (EXEMPLAR)	Varies. May be very specific.	Yes.	Deviance occurs, but innovation may not constitute deviance.	Exemplar Extension.

Figure 14

Comparison of Exemplar, Norm, and Expectation.

(This is general only. The text should be consulted for details).

discussion, but has used Kuhn's novel vocabulary.

It is possible that some of these features of social control as envisaged by Kuhn, have wider application than simply to science. Wherever innovation occurs, there are certainly problems in exclusive description in terms of normative systems of social control. Again, although direct modelling as a process has some obvious difficulties related to its inaccessibility to linguistic description, it may occur in areas of social life other than science. I am implying that, whether or not these features of exemplary systems of social control can be reclaimed and subsumed to the term norm, that none the less at the present they highlight aspects of the process that deserve more attention than they typically receive.

11.6 Conclusion

The general conclusion to be drawn from the theoretical scheme outlined in the previous sections may be stated quite simply: the ease with which new standards are developed and accepted depends on the nature of existing standards. Where the exemplar set and the most important aspects of specialist identity relate to methodological standards, then there will be a stronger distinction between permissible and impermissible methods, and greater freedom about areas of work. Where the exemplar set and the most important facets of specialist identity relate to theoretical standards, then the areas of work and the methods employed will be less directly controlled. It is in these latter areas that some types of work will be preferred, and others less preferred, and as has been seen in the discussion above, the factors that determine the permissible and the impermissible areas are not the same as those that determine

the preferred and non preferred. Any understanding of the reasons for the direction of scientific growth must begin with an understanding of this distinction.

The relationships discussed above have been outlined in Figure 14. In this figure arrows indicate lines of influence, and double arrows indicate a close relationship whose nature is not necessarily completely specified. Figure 15 uses the scheme outlined in Figure 14 and applies it to X-ray crystallography. The result is only very general, but it indicates the sort of factors that have to be considered.

This terminates the main theoretical discussion in this thesis. In the following section the theoretical scheme is further illustrated in relation to the data on X-ray crystallography assembled in Chapters 2 - 9. In the concluding section, some suggestions for further research are offered. Before moving on to these sections a brief warning about the status of the theoretical scheme should be offered.

The scheme does not offer an explanation for the direction of scientific growth under normal science situations. It fails to do this for a number of reasons. Firstly, its scope is much more limited -- it does not cover what have been called "external" factors that affect scientific growth. Secondly, and perhaps more fundamentally, the scheme outlines some of the factors that operate in defining the direction of scientific growth, but it does not in turn analyse them and try to understand the way in which they are set up. Thus, the term exemplar set is extensively used, yet to explain the direction of scientific growth of a specialty in terms of an exemplar set is not in fact to offer an explanation -- it is rather to offer

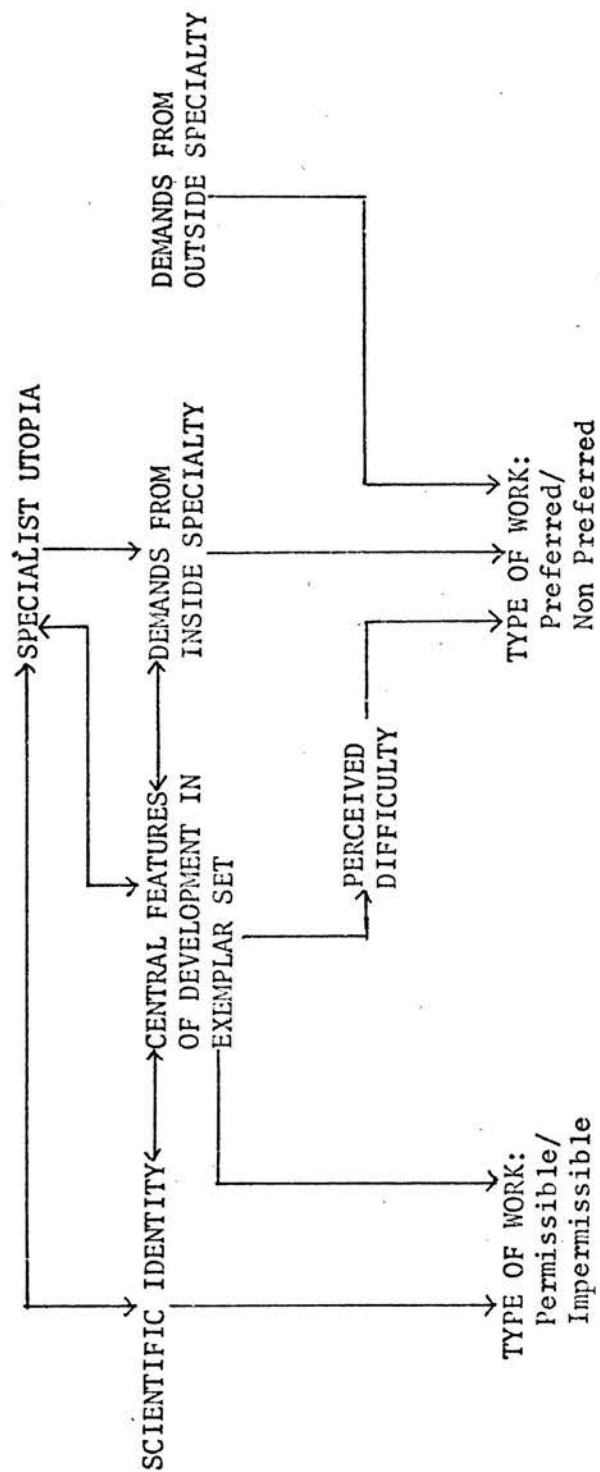


Figure 15

Representation of Theoretical Scheme

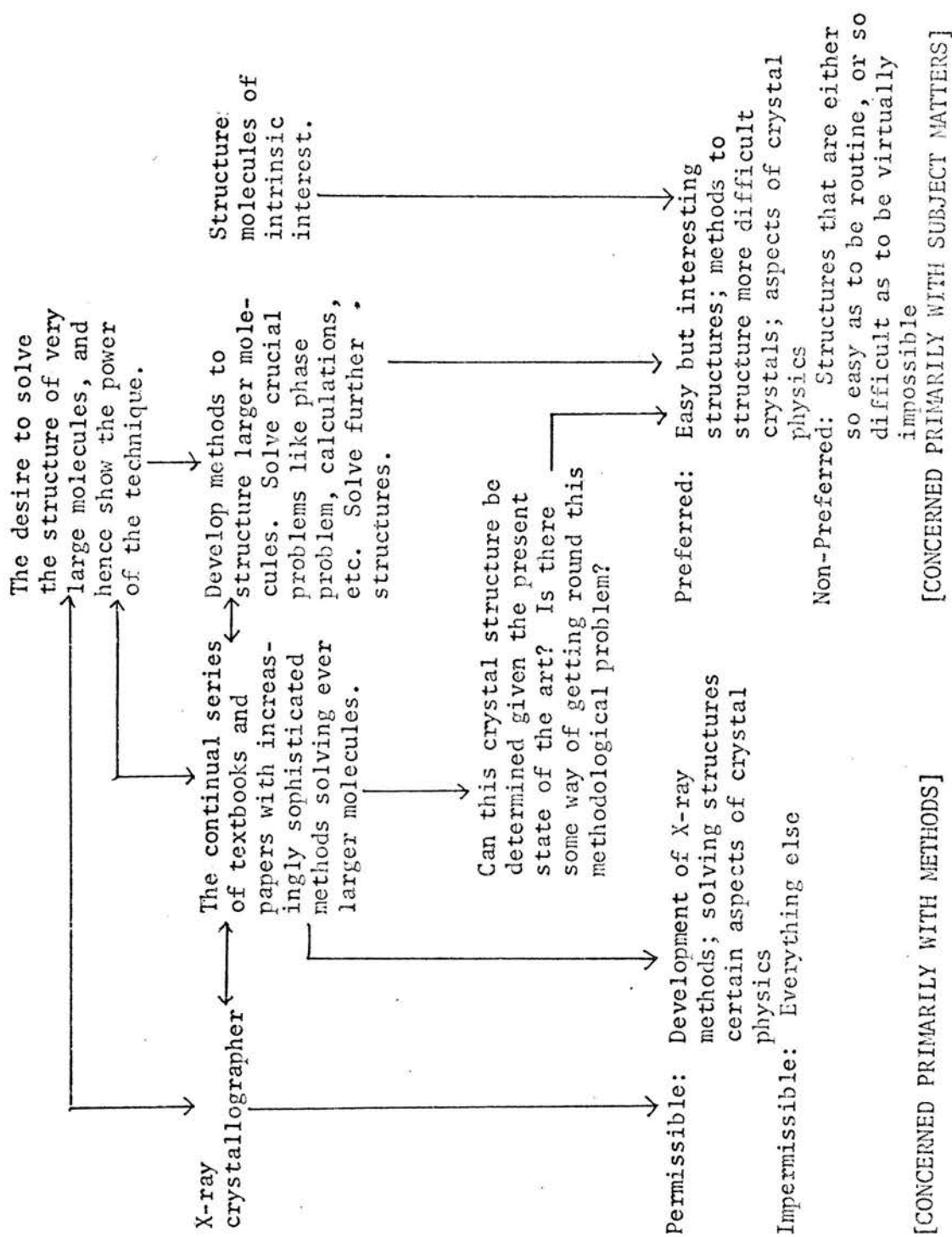


Figure 16

Theoretical Scheme as Applied to Methods Based Specialty

a partial redescription. It is a redescription that is amenable to further analysis -- more so, I would argue, than the original question about the direction of scientific growth. Thus, exemplar sets can be determined over time, and the way in which they become established in relation to basic features of the system of scientific socialisation can be examined. When this happens, then we shall have moved from a theoretical description to something that looks more like an explanation.

Thus, the theoretical scheme does not "explain" the reasons for the direction of scientific growth. It describes it in a "theory heavy manner" -- a manner that hopefully poses presently untouched but hopefully amenable questions which can be answered through further study.

11.7 The Illustration of the Theoretical Scheme

No attempt will be made to offer a complete account of the data concerning the history of X-ray crystallography that was presented in Chapters 2 - 9. Rather, the theoretical scheme is used to suggest that certain classes of data and events have importance and significance in their own right, and furthermore may be seen as being connected with one another in ways fully or partially specified.

Thus particular significance may be attached to

1. the scientific identity of *workers* identified in the area of X-ray crystallography.
2. the central features of the development of the exemplar set, together with other aspects of the specialist matrix such as the nature of the symbolic generalisations and the identification of values.

3. the nature of the demands for work made by workers who can properly be seen as within the specialty.

4. the nature of the demands of those workers who are outside the specialty.

5. the nature of the specialist utopia.

11.71 Identification of British X-ray Crystallography as a Technique Based Specialty

Evidence to suggest that British X-ray crystallography constituted a technique based specialty has already been presented in earlier sections. This will be very briefly summarised.

1. X-ray crystallography in Britain was a specialty in that a group of workers (a) shared cultural orientations, and (b) were in communication with one another, so that they formed the "primary locus of social control".

The fact that they shared cultural orientations can be seen from the fact that a group of early workers (Bernal, Astbury, Lonsdale, Gibbs, Shearer, Cox, and Robertson at the Royal Institution, and Bradley, James, Williams, Taylor, West, Jay, Brindley at Manchester) underwent similar training and work in X-ray crystallography under the Braggs. It can also be seen in the nature of the work that they carried out, which depended on a specialist matrix set up by Laue, the Braggs and their pupils. Although within the group of British workers there was specialisation in terms of the types of crystals studied, there was none the less interchange of methods, and many important pieces of work were exemplary for the whole community. The fact that workers were in touch with one another can also be deduced from the above.

2. It was technique based in that the specialist matrix and

the exemplar set at any given time, or the movement of the exemplar set over time, all concentrated on a particular method -- that of X-ray crystallography -- and how that method might be made more powerful.

Can it be suggested that the developments constitute as much developments in theory as in techniques? While this is one possible way of explaining them, there are two reasons why this is unsatisfactory:

1. The goal of the crystallographers was two fold -- to determine the structures of crystals, and to develop methods. Obviously these two are very closely connected, and this can be seen, for example, in the case of the protein workers. Their main goal was to determine the structure of a protein, and the methodological and technical work was done in order to approach that goal.

2. In any case, there were no great advances in physical theory which resulted from X-ray crystallographic work after the late 1920s. For while the F curve calculations were of relevance to physical work on the nature of the atom, by 1930 the main lines of crystallographic work had been laid down -- the problems were reasonably clear -- what was required was solutions. When these solutions came they did not normally involve fundamental innovation. They were in the nature of normal science articulations that grew out of phenomena or ideas that were already well known.

The fact that there was a well defined specialist matrix can be seen from the early textbooks (such as X-rays and Crystal Structure by the Braggs). The exemplar set, both in this and other textbooks, and in research papers concentrated on the development of the method.

The contributions of workers to the development of methods has already been extensively described in the empirical chapters of this thesis. It will be recalled that W.L.Bragg reproduced a list of achievements in the period 1912 to 1920 (Bragg W.L.:1970a:172) which included: the discovery of the wavelength of X-rays; the analysis of simple crystals; the accurate measurement of intensities; the measurement of the Debye effect; the calculation of the reflections by perfect and mosaic crystals; the development of the powder method; the realisation of the fact that each crystal diffraction pattern corresponds to a Fourier component of electron density in the crystal.

The catalogue of improvements in techniques in the twenties and thirties is long and impressive. Improvements included the development of photographic methods, including especially the development of rotation photography which was introduced to a wide English speaking audience in 1926 by Bernal; further developments in intensity measurements; development of better X-ray tubes; the development of the "space group tables"; the development of Fourier methods; the development of the isomorphous replacement methods; the development of understanding of packing arrangements in crystals (including the development of calculations for atomic radii); the growth of understanding in the area of the theory of X-ray intensities; the development of international collaboration which resulted in the use of standard terminology; the structuring of many crystals, including major work on inorganic, mineral, organic, and metal structures.

Coming forward to the work on proteins, the solution of a major series of technical problems has also been an important feature of this work. Thus, it will be recalled that in Chapter Seven, five major problems were outlined, and these were all overcome (or found

to be illusory). The five were: the difficulty of taking good X-ray diffraction photographs of globular proteins; the impossibility of getting round the phase problem by means of trial and error methods; the problems of measuring large numbers of intensities; the problems associated with the handling of large quantities of data; the difficulties of developing meaningful and interpretable electron density maps from the available data.

Most of the developments that have been mentioned above resulted in the removal of a bottleneck -- a problem that was holding up work in a particular area -- in the language of Kuhn, they were puzzle solutions. Thus, to take one of the most obvious examples, that of the work by Bernal on the wet pepsin crystal photographs, this opened up the whole area to the full range of sophisticated X-ray diffraction techniques. Before 1934 the only photographs obtainable showed little evidence of high order, and were completely uninterpretable. After Bernal's work it was possible to see that there was atomic detail in the photographs, and it was possible to determine the size of the unit cell and the molecular weight of the protein. While in the absence of a knowledge of the phases, it was impossible to determine the molecular structure, it none the less opened the road to many Patterson analyses that were calculated in the late thirties and fourties. The work in the whole crystalline protein tradition was dependent on Bernal's work.

Similarly, the success of the isomorphous replacement method in finally getting round the phase problem constituted another major technical advance, opening up the area, and leaving no major problems between the protein workers and the successful determination of protein structures.

These two examples, which together with many more, were fully described in the empirical chapters, are taken from the above list as examples of the way in which these events, in many cases, constituted technical advances, increasing the power of the X-ray method.

Examination of a modern textbook of X-ray crystallography constitutes further evidence of the existence of a specialist matrix, and an exemplar set. Thus one recent textbook Chemical Crystallography by Bunn, covers the following subjects: crystal morphology; optical properties of crystals; crystal microscopy; identification by powder X-ray photography; determination of the unit cell by X-ray diffraction; determination of atomic positions by trial and error; other physical methods, and their application to structure determination; examples of X-ray diffraction and structure determination by trial and error; direct and semi direct methods of crystal analysis (including determination of phases angles, Patterson maps); small angle scattering, and effects on diffraction caused by varying crystal size.

This goes a long way towards supporting the assertion that British X-ray crystallography may be seen as a technique based specialty. When this is combined with the fact that intercommunication was maintained at least until the late fifties between workers studying different kinds of crystals ¹, a good case has been made out for the

1. Consider, for example, the remarks by Phillips about attending the XRAG meetings despite the scoffing (Chapter 9), the fact that several of the protein workers also did work on non proteins, and the fact that some non protein crystallographers were sympathetic to protein crystallography.

proposition that British X-ray crystallography constituted from 1918 onwards, a technique based specialty.

11.72 The Direction of Growth of British X-ray Crystallography

If British X-ray crystallography constitutes an example of a technique based specialty, then it follows that certain types of data become of particular importance. Thus, if the theoretical scheme is correct, it should indicate that

1. There was a fairly clear distinction between permissible and impermissible methods, and their uses.
2. There was a more flexible attitude towards the types of crystals that might be structured.
3. That the types of crystals chosen depended partly on the state of development of the methods, and partly on demands from outside the specialty.
4. That workers tended to identify themselves as crystallographers.
5. That they expressed aspects of a specialist utopia concerning the development of methods, and the structuring of large or difficult crystals.

Given the presented data, these propositions can be supported in varying degree.

11.721 Permissible and Impermissible Methods

It has been seen that a great proportion of the work carried out has related to the improvement of methods. Most of this clearly falls into the permissible bracket. There is only one major exception, and this relates to the work of Dorothy Wrinch on the interpretation of Patterson diagrams. Here, it will be recalled that certain central figures in the specialty felt that her work was so badly off the rails that they felt enjoined to write letters to

Nature about the subject. This may be taken as a very strong form of negative sanctioning, and it indicates, in this case at least, that the standards in question were seen as being important. Of particular interest in the context was a remark made by W.L.Bragg, who wrote at one point:

Exaggerated claims as to the novelty of the geometrical method of approach and the certainty with which a proposed detailed model is confirmed are only too likely, at this stage, to bring discredit upon the patient work which has placed the analysis of simpler structures upon a sure foundation.

(Bragg W.L.:1939:74)

This suggests that Bragg felt a sense of identification with the technique of X-ray crystallography, and that this was responsible for the strength of his condemnation of this (to him erroneous) line of development.

Although this case is the only example of formally sanctioned action that has come to light in this respect, the fact that none other has been discovered may, in the right circumstances, be seen as further proof of the strength of the attitudes attaching to methods, and the depth and thoroughness of the scientific socialisation procedures that underlie those attitudes. One might hypothesise that breaking the standards would normally result in strong informal sanctioning, which might be difficult to discover at this length of time after the event. Only an actor who was more than normally isolated from the other actors in the specialty, or who was exceptionally strong willed and independent, would none the less continue along a line of work that was unacceptable to the majority.

Thus, it may be argued that the development of British X-ray crystallography consists, in large part, of the development of a series of methods that bear a strong relationship to one another;

the development of a new method is met with acute scrutiny by other members of the specialty, who accept or reject it in accord with their own existing methodological standards and perceived problems. The fact that most of the workers used these techniques in their own work, and therefore knew them intimately well, and were also very dependent on them, would underline the proposition that considerable conformity would be expected in this direction.

Most of the work that was not on the development of methods, was on the determination of structures; it can be seen (and has been shown in the empirical chapters) that workers tended to stick to the technique of X-ray crystallography, and not to use non-crystallographic techniques. In some cases, the techniques were supplemented by other assumptions, physical or chemical, but none the less the bulk of the work can truly be said to be crystallographic.

In a sense, then, with the exception of the Wrinch controversy, the evidence for the strength of the delineation between permissible and impermissible methods, and permissible and impermissible use of those methods is negative. The fact that most crystallographers stuck to X-ray crystallography, and did not make extensive use of other methods, and the fact that most work on methods that was published was acceptable, can be seen as negative evidence for the proposition that there were very strong standards (and very efficient training processes) that stopped workers from straying into impermissible work on methods.

11.722 Preferred and Non Preferred Areas

It has been argued that there is much more leeway to work on different subject matters. Attitudes to methods affect the nature of the work area chosen in two ways. Firstly, the nature of the

technique automatically rules out work on certain classes of substances. Thus, one would expect to discover that crystallographers studied materials that were crystalline, or semi-crystalline, and this is normally the case. Secondly, the state of development of the exemplar set, and the other aspects of the specialist matrix would clearly affect the perceived difficulty of the class of substances to be tackled, and this would affect the type of work the actor would carry out. This is also found to be the case. W.L.Bragg had a rather amusing quantitative way of demonstrating that the substances being structured were getting more difficult as the years passed. He charted the number of parameters to be determined in any crystal on a logarithmic scale, and the result was quite a smooth, but consistently ascending slope, starting at one in 1913, going through one hundred in 1935, to about 300 in 1955, to about 10,000 in 1960. With the breakthrough of heavy atom methods in the protein field in the late fifties, the smooth curve shot upwards. Although this graph (Ewald :1962:135) does not indicate which structures were attempted, it does give some indication of the order of difficulty of those that were being determined, and therefore acts as a guide to the power of the technique.

Assuming, however, that the areas chosen depended partly on the demands made on the actors by other actors, then one would expect to find a concentration in certain areas which were seen as being important. These would, in part, relate to structures that were seen as being "ripe" for examination, and partly there would be demands from outside the specialty for the worker to study crystals that were of intrinsic importance. Thus, although the demand for work in the areas of inorganic, organic, and metal structures has not been

determined, it was clear from the limited empirical material presented in Chapter 8, that there existed a demand from certain quarters to know more about the structures of proteins.

It will be recalled that a number of different attitudes to the work on proteins in the late thirties were outlined. These attitudes were then traced through the forties and fifties in the form of the actions of the workers concerned. It will be recalled that workers interested in proteins constituted only a small group amongst a larger group of X-ray crystallographers who were interested in all subjects. Thus, it was suggested that the protein workers in the late thirties constituted, if not a deviant group, at least a group that was working on an unpopular subject matter.

Further, it was suggested that the various attitudes to protein crystallography can be seen, in most cases, as being the result of different interpretations of a purely crystallographic tradition. Thus, it was suggested that in each case the reasons for these different attitudes rested on different estimates of the likelihood of success of different strategies for work on the proteins. It will be recalled that the attitudes outlined were those exemplified the expressed opinions and/or work of Perutz, Hodgkin, Bernal, Pauling, non protein crystallographers, Astbury, and finally workers from other specialties who were interested, for their own reasons, in the structures of proteins. In the case of Perutz, Hodgkin, and the non protein crystallographers, it was suggested that the main reasons for their attitudes were almost entirely crystallographic, and became more so as time passed. In the case of Pauling, they were partly crystallographic, but also rested on criteria drawn from structural chemistry. In the case of Astbury the criteria were no

longer crystallographic, but became increasingly "molecular biological".

Thus, all the approaches outlined, with the exception of the non crystallographers, Astbury (and to some extent Pauling), were concerned with the development of methods -- a pushing forward of the "state of the art". Perutz, it will be recalled, was perhaps the most optimistic, and tried to push Patterson and swelling and shrinking methods to the limit, before having his attention drawn to the isomorphous replacement method. These methods were all articulations of the central standards of X-ray crystallography, and the standards constituted exemplary procedures for deriving structures from diffraction patterns. As such, they related to conditions for taking diffraction readings, and conditions for moving from the data to the structure. Perutz' problem was to develop and apply the existing exemplars to situations that were beyond the routine, and being less fearful of the great complexity of the proteins than most of his colleagues, he chose to study haemoglobin from the start.¹

Hodgkin, unlike Perutz, developed methods in relation to simpler molecules -- molecules which were, for this reason, simpler to structure. This involved, in many respects, a similar approach to that of Perutz. Thus, Hodgkin was concerned to extend symbolic generalisations through the development of new and revised exemplary applications, to situations that were novel in certain respects. Her strategy, as has been pointed out, was to work from simpler to more

1. However, he did not formulate the determination of the structure of haemoglobin as a goal from the start; none the less he spent the bulk of his working life from 1937 to 1960 and beyond trying to discover more about the structure of the molecule than was currently known, by means of X-ray diffraction.

complicated molecules, feeling that it was by smaller steps that the required exemplars might be best developed. Bernal, whose appreciation of the problem was in important respects similar, also tried to develop methods. His approach was to step back and develop certain important techniques by separate programmes of research.

Pauling's attitude was unlike any of the three mentioned above. He proposed to apply existing exemplars to determine the structures of component parts of the proteins. Having once determined these parts he proposed to apply methods developed from his study of physical chemistry to build models of whole proteins.

Bernal, Hodgkin, and Perutz were all, thus, crystallographers who worked in relation to certain crystallographic standards, to develop and articulate those standards in order to solve protein structures. Even Pauling's approach can be seen to be partially crystallographic -- model building, after all, being an accepted procedure in the crystallographic community -- although Pauling would not have considered himself a crystallographer, but rather a structural chemist.

The array of attitudes to the protein work displayed by non protein crystallographers can be similarly explained by different appreciations of the relationship between the problems being posed (i.e. the attempts to solve structures of proteins) on the one hand, and the available means on the other (i.e. the exemplary set, and other aspects of the specialist matrix). Thus Robertson could see the possibility that the method that he had been most important in developing (the heavy atom method) might one day provide a means of determining the structures of proteins, and for this reason, although he did not engage on any work on the proteins himself, he always

maintained a supportive attitude to those who worked on proteins. There were others, whose position has been outlined, who thought that the technical problems were so great that the likelihood of success was close to zero. For this reason they became what Phillips called the "scoffers".

It can be seen, therefore, that those who were within a crystallographic tradition had attitudes to protein work that can first and foremost be interpreted in terms of that tradition. Although this aspect of the work cannot be systematically discussed here, it is interesting to note that even within a tradition as tight and rigorous as X-ray crystallography, there was still wide room for manoeuvre, and different attitudes to the same piece of work. Here the preferred area of work was dependent, in large measure, on largely shared crystallographic standards. How these standards were interpreted depended in part on the personality and situation of the actor.

The above remarks do not, in many respects, apply to Astbury, however. If crystalline proteins constituted in some respects a permissible area, then the fibrous proteins verged on the impermissible. Thus, it will be recalled that Bernal and a number of his colleagues and former colleagues at the Royal Institution were "shocked" at Astbury's move into textile physics, feeling that it was "very premature" to enter this complex and mundane field, at least until the structures of regular crystals had been more fully understood.

In the main account above, it was pointed out how Astbury was always very keen -- even more so than Bernal -- to see interdisciplinary communication, and he wished to make use of all possible approaches to the understanding of proteins. Quotations from the main text

indicate that for workers such as Hodgkin, the importance of the protein community in actually affecting the manner in which the work was carried out was very slight -- she was first and foremost a crystallographer. This was not so for Astbury. It was shown how he came to use other techniques -- notably electron microscopy -- and no longer looked upon himself as primarily a crystallographer -- that he came, in effect, to call himself a molecular biologist. It is suggested that Astbury, unlike the other workers, became primarily attached to a subject matter rather than a technique, and although he continued to use X-ray crystallography, this was only one of a number of different possible techniques.¹ The reasons for Astbury's change of identity cannot be fully discussed here, but of great importance must have been the inadequacy of X-ray crystallographic methods in the face of fibrous proteins, and the fact that Astbury, in a cross disciplinary department, had an anomalous colleague group including wool chemists. Astbury's work was by no means fully acceptable to other protein crystallographers -- his approach was criticised, although not publically, by both Perutz and Fankuchen. Although Astbury was not the object of very strong negative sanctioning, because he did not positively carry out crystallographic procedures in a manner which was unacceptable and seen to be wrong by the community (as for example did Wrinch), his work was not particularly acceptable because it depended heavily on other techniques.

The above interpretation of different attitudes to protein work is

1. It is possible that one or two of the other protein workers have now reached approximately the same point of view, but thirty or forty years later, after successful pursuit of the crystallographic goal.

based on the distinction, made in the theoretical discussion above, between permissible and impermissible types of work on the one hand, and preferred and non preferred types of work on the other. It was suggested that the factors which influence these two are different, and that in the case of the technique based specialty, the exemplar set, and hence the standards of acceptable work, are concerned first and foremost with methods, and their appropriate use, while the factors influencing subject matters are more diverse, and relate in part to the state of development of the methods, and in part to demands from outside the specialty. No systematic evidence has been presented about the demands from outside the specialty. However, the varying ways in which an exemplar set oriented primarily to methods influenced attitudes to protein work, were spelled out in detail in Chapter 8 and have been outlined above in more theoretical terms.

11.73 Conclusion

The extent to which the theoretical scheme can be tested or illustrated is limited by the fact that it was developed in relation to the main study on X-ray crystallography. However, general data presented in the main section depicted British X-ray crystallography as a concern, originally headed by the two Braggs, which at most stages throughout its development has been reasonably cohesive. It further presented a picture of the continuous development of X-ray crystallographic techniques over a period of nearly half a century. The successful development of these techniques was illustrated by the fact that much more complicated structures came to be successfully determined over time. It was shown that substantial numbers of workers spent many years working in this area, and that they constituted groups that were not in fundamental methodological

disagreement with one another. This data, which was presented in detail, acts as a background for the above theoretical discussion. The points that have been highlighted in the section immediately above, where the theoretical scheme has been applied in some detail to certain parts of the data, should be seen as particular instances where it has been especially easy to illustrate the scheme.

11.8 Suggestions for Future Research

It can be argued, without discussing in detail what constitutes a theory in sociology, that the above account offers a theoretical description of a part of normal science. Certainly, in the manner in which this thesis has been conceived and written, it cannot be said to have survived any process analogous to Popperian conjecture and refutation. Suggestions for future research fall, essentially, into two classes. There are those suggestions that aim to check the scheme, first and foremost. Then there are those suggestions that aim to extend it, and further specify the causal relationships affecting some of the terms that have been used above.

The desire to test the scheme implies that the author does not feel that his present work is satisfactory, and this of course, is so. Without looking for difficulties, it should none the less, perhaps, be indicated that much of the historical work done in connection with this thesis (and certainly much excluded from the final draft) need not, in terms of the foci of interest of the scheme, have been carried out. Conversely, certain classes of data not collected during the course of the study, would now turn out to be very interesting. None the less, with the theoretical interests emerging in the course

of the study, the fact that a scheme of the sort developed above has grown up suggests to the author that the study has not been in vain.

The wish to test the scheme can be implemented in a number of ways, but specifically depend on a more comparative approach than the one which has been developed above. If the scheme is to be tested in this way, then it will be necessary to match two areas of science, for both points of similarity and dissimilarity, and determine whether these dissimilarities, seen in the context of the scheme, result in a reasonable description of the separate paths of growth of the two areas. Even better would be an approach which drew certain implications from a general theory that were in conflict with the assumptions in the scheme developed above. It would then be possible to compare the predictions of the one with the predictions of the other.

There are two obvious possibilities which correspond to the two possible implementations mentioned above. The first, which corresponds to the comparison of two matched, but different, areas of science, would involve a comparison of the work of the German physicists who worked on X-ray crystallography with that of the British workers. It has been suggested that the former might be seen as an example of a theory based specialty, and the latter as an example of a technique based specialty. If this is so, then there will be important differences in their exemplar sets, even though they would be expected to overlap. Also, the specialist utopias would be different. In an account of the divergent paths of the two groups of workers from what might seem to be common origins, one would concentrate on the workings of the scheme described above, and the dissimilarities of the exemplar sets. Further, one would

inquire into the dissimilarities in the exemplar sets, thus taking the examination one step back, and attempting a causal explanation of the nature of the exemplar set.

The other approach would involve the comparison of another theory, with the predictions and assumptions of the above scheme. Thus, one might argue (although this would have to be done in detail), that Kuhn's theory provides few guidelines about the direction in which a paradigm or a specialist matrix might develop, and hence implies that it would develop in all possibly articulable directions simultaneously. The import of the scheme that has been developed is that this is not what happens, in fact; it would be necessary to show, in an empirical case, why the direction of growth was predominantly concentrated in a few areas, and why other areas were not developed at all.

A further and obvious way of developing this research depends on the fact that a typology has been set up which allows for different types of specialty formation (i.e. does the social network precede the successful piece of work, or vice versa?) If research of this type is to be developed, it is necessary to concentrate as much on the nature of the developing interaction nets as it is on the cultural change. It is only if this line of work is pursued that it will be possible to discover whether the notion of the problem based specialty, developed in the above text, has in fact any utility. So in future research it will be necessary to make systematic studies of important scientific communication nets in much the same way as has recently been carried out by Mullins. In this way we may develop insights into the range of empirical possibility in the formation of new specialties.

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